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U pacjentów z rakiem gruczołu krokowego z przerzutami opornym na kastrację, niepoddającym się leczeniu operacyjnemu, otrzymujących tryptorelinę oraz kwalifikujących się do leczenia inhibitorami biosyntezy androgenów, leczenie tryptoreliną powinno być kontynuowane. **Przeciwwskazania:** Nadwrażliwość na GnRH, jej analogi lub na którąkolwiek substancję pomocniczą. Stosowanie tryptoreliny jest przeciwwskazane w okresie ciąży i karmienia piersią. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** Stosowanie analogów GnRH może zmniejszać gęstość mineralną kości. U mężczyzn wstępne dane wskazują, że stosowanie bisfosfonianów w skojarzeniu z analogami GnRH może zmniejszyć utratę gęstości kości. Zachowanie szczególnej ostrożności jest konieczne u pacjentów z dodatkowymi czynnikami ryzyka osteoporozy (np. przewlekłe nadużywanie alkoholu, palenie papierosów, długoterminowa terapia lekami zmniejszającymi gęstość mineralną kości, np. leki przeciwdrgawkowe lub kortykosteroidy, dodatni wywiad rodzinny w kierunku osteoporozy, niedożywienie). W rzadkich przypadkach stosowanie analogów GnRH może ujawnić obecność wcześniej nierozpoznanego gruczolaka wywodzącego się z komórek gonadotropowych przysadki. U pacjentów tych może wystąpić udar przysadki, objawiający się nagłym bólem głowy, wymiotami, zaburzeniami widzenia i porażeniem mięśni oka. Istnieje zwiększone ryzyko wystąpienia epizodu depresyjnego (z możliwymi przypadkami ciężkiej depresji) u pacjentów będących w trakcie leczenia agonistami hormonu uwalniającego gonadotropinę, takich jak tryptorelina. Pacjentów należy odpowiednio poinformować i leczyć w zależności od występujących objawów. Pacjenci z depresją powinni być ściśle kontrolowani podczas terapii. Na początku leczenia tryptorelina, podobnie jak inne analogi GnRH, powoduje przemijający wzrost stężenia testosteronu w surowicy. W rezultacie, sporadycznie, w pierwszych tygodniach leczenia w pojedynczych przypadkach rozwijało się przemijające nasilenie przedmiotowych i podmiotowych objawów raka gruczołu krokowego. W początkowej fazie leczenia należy rozważyć dodatkowe podanie odpowiedniego antyandrogenu, aby przełamać początkowy wzrost stężenia testosteronu w surowicy i nasilenie objawów klinicznych. U niewielkiej liczby pacjentów może dojść do przejściowego nasilenia podmiotowych i przedmiotowych objawów raka gruczołu krokowego (przejściowe zaostrzenie objawów nowotworu) i przejściowego nasilenia bólu związanego z chorobą nowotworową (ból związany z przerzutami), które można leczyć objawowo. Podobnie jak w przypadku innych analogów GnRH obserwowano izolowane przypadki ucisku (kompresji) rdzenia kręgowego lub niedrożności cewki moczowej. Jeżeli rozwinie się ucisk (kompresja) rdzenia kręgowego lub niewydolność nerek, należy wdrożyć standardowe leczenie, a w ekstremalnych przypadkach należy rozważyć wykonanie pilnej orchidektomii (usunięcie jądra). W pierwszych tygodniach leczenia wskazane jest staranne monitorowanie terapii, szczególnie u pacjentów z przerzutami do kręgosłupa, narażonych na ryzyko ucisku rdzenia kręgowego oraz u pacjentów z niedrożnością układu moczowego. Po kastracji chirurgicznej tryptorelina nie indukuje dalszego zmniejszenia stężenia testosteronu w surowicy. Długotrwała deprywacja androgenu, zarówno po obustronnej orchidektomii (usunięcie jądra), jak i po podaniu analogów GnRH, związana jest ze zwiększonym ryzykiem utraty masy kostnej i może prowadzić do osteoporozy oraz wzrostu ryzyka złamań kości. Deprywacja androgenowa może wydłużać odstęp QT. U pacjentów z występującym w wywiadzie wydłużeniem odstępu QT lub z czynnikami ryzyka jego wystąpienia, jak również u pacjentów otrzymujących leczenie towarzyszące, które może powodować wydłużenie odstępu QT lekarz powinien oszacować stosunek korzyści do ryzyka, w tym możliwość wystąpienia zaburzeń rytmu serca typu torsade de pointes, przed włączeniem produktu leczniczego Diphereline SR 11,25 mg. Ponadto, w badaniach epidemiologicznych obserwowano, że u pacjentów może dojść do zmian metabolicznych (np. nietolerancja glukozy, stłuszczenie wątroby) lub może zwiększać się ryzyko choroby układu krążenia w czasie terapii z deprywacją androgenu. Jednakże prospektywne dane nie potwierdziły związku pomiędzy analogami GnRH i wzrostem śmiertelności z przyczyn sercowych. Pacjentów z dużym ryzykiem chorób metabolicznych i chorób układu krążenia należy starannie ocenić przed włączeniem leczenia i w odpowiedni sposób kontrolować w czasie terapii z deprywacją androgenu. Podawanie tryptoreliny w dawkach terapeutycznych powoduje supresję osi przysadkowo-gonadalnej. Normalna funkcja powraca zwykle po zaprzestaniu leczenia. Dlatego testy diagnostyczne gonadalnej funkcji przysadki w czasie leczenia i po zaprzestaniu terapii za pomocą analogów mogą być mylące. Na początku leczenia stwierdza się przemijające zwiększenie aktywności fosfatazy kwaśnej. W czasie leczenia zaleca się przeprowadzać ocenę reakcji układu kostnego za pomocą scyntygrafii i (lub) tomografii komputerowej, natomiast ocenę reakcji gruczołu krokowego na leczenie przeprowadza się za pomocą USG i (lub) tomografii komputerowej oraz badania klinicznego i *per rectum*. Skuteczność leczenia może być monitorowana poprzez oznaczanie stężenia testosteronu i antygenu specyficznego dla prostaty w surowicy krwi. Ten produkt leczniczy zawiera mniej niż 1 mmol (23 mg) sodu na dawkę, to znaczy produkt leczniczy uznaje się za „wolny od sodu". **Działania niepożądane:** Ponieważ pacjenci z miejscowo zaawansowanym lub przerzutowym zależnym od hormonów rakiem gruczołu krokowego są zazwyczaj osobami w starszym wieku i występują u nich inne choroby typowe dla wieku podeszłego, działania niepożądane leku zgłosiło ponad 90% pacjentów uczestniczących w badaniach klinicznych, ocena istnienia związku przyczynowego między stosowanym lekiem a występującym objawem jest trudna. Podobnie jak w przypadku leczenia z udziałem innych agonistów GnRH lub po kastracji chirurgicznej, najczęściej obserwowane działania niepożądane związane z leczeniem tryptoreliną spowodowane były przewidywanym działaniem farmakologicznym. Działania te obejmowały uderzenia gorąca i spadek libido. Wszystkie zdarzenia niepożądane z wyjątkiem reakcji immuno-

alergicznych (rzadko) oraz odczynów w miejscu podania wstrzyknięcia (<5%), są związane ze zmianą stężenia testosteronu. Uznano, że zgłoszone następujące działania niepożądane były prawdopodobnie związane ze stosowaniem tryptoreliny. O większości z nich wiadomo, że są związane z biochemiczną lub chirurgiczną kastracją. Częstość występowania działań niepożądanych została sklasyfikowana w następujący sposób: bardzo często (≥ 1/10); często (≥ 1/100 do < 1/10); niezbyt często (≥ 1/1000 do < 1/100.); rzadko (≥ 1/10 000 do < 1/1000). *Bardzo często:* osłabienie, ból pleców, parestezje w kończynach dolnych, zmniejszenie libido, zaburzenia erekcji (w tym brak wytrysku, zaburzenia wytrysku), nadmierna potliwość, uderzenia gorąca; *Często:* uczucie suchości w jamie ustnej, nudności, odczyn w miejscu wstrzyknięcia (w tym rumień, zapalenie i ból), obrzęk, nadwrażliwość, zwiększenie masy ciała, ból mięśniowo-szkieletowy, ból kończyn, zawroty głowy, ból głowy, depresja*, utrata libido, zaburzenia nastroju*, ból miednicy, nadciśnienie tętnicze; *Niezbyt często:* trombocytoza, kołatanie serca, szum w uszach, zawroty głowy, upośledzenie widzenia, ból brzucha, zaparcie, biegunka, wymioty, letarg, obrzęki obwodowe, ból, dreszcze, senność, zwiększona aktywność aminotransferazy alaninowej, zwiększona aktywność aminotransferazy asparginowej, zwiększone stężenie kreatyniny we krwi, wzrost ciśnienia tętniczego krwi, zwiększone stężenie mocznika we krwi, zwiększona aktywność gamma-glutamylotransferazy, spadek masy ciała, jadłowstręt, cukrzyca, dna moczanowa, hiperlipidemia, zwiększenie apetytu, ból stawów, ból kości, skurcze mięśni, osłabienie mięśniowe, ból mięśniowy, parestezje, bezsenność, drażliwość, nokturia, zatrzymanie moczu, ginekomastia, ból sutków (gruczołów piersiowych), atrofia jąder, ból jąder, duszność, krwawienie z nosa, trądzik, łysienie, rumień, świąd, wysypka, pokrzywka; *Rzadko:* nieprawidłowe uczucie w obrębie oczu, zaburzenia widzenia, wzdęcia, zaburzenia smaku, wzdęcia z oddawaniem wiatrów, ból w klatce piersiowej, trudność w utrzymaniu pozycji stojącej, objawy grypopodobne, gorączka, reakcja anafilaktyczna, zapalenie jamy nosowej i gardła, zwiększona aktywność fosfatazy alkalicznej we krwi, sztywność stawów, obrzęk stawów, sztywność układu mięśniowo-szkieletowego, zapalenie kości i stawów, zaburzenia pamięci, stan splątania, zmniejszenie aktywności, euforyczny nastrój, duszność w pozycji leżącej, powstawanie pęcherzy, plamica, spadek ciśnienia; *Dodatkowe działania niepożądane stwierdzone w okresie po wprowadzeniu do obrotu - częstość występowania nieznana: wydłużenie odstępu* QT (*Częstość występowania podano na podstawie częstości występowania wspólnej dla całej klasy agonistów GnRH*), udar przysadki (*Działanie niepożądane zgłaszane po pierwszym podaniu u pacjentów z gruczolakiem przysadki*), złe samopoczucie, wstrząs anafilaktyczny, niepokój, nietrzymanie moczu, obrzęk naczynioruchowy. Tryptorelina powoduje przemijający wzrost stężenia krążącego testosteronu w ciągu pierwszego tygodnia po pierwszej iniekcji postaci o przedłużonym uwalnianiu. Przy takim początkowym wzroście stężenia krążącego testosteronu u niewielkiego odsetka pacjentów (≤ 5%) może dojść do przemijającego nasilenia podmiotowych i przedmiotowych objawów raka gruczołu krokowego (przejściowe zaostrzenie objawów nowotworu), które zwykle objawia się nasileniem objawów ze strony układu moczowego (< 2%) oraz bólu związanego z obecnością przerzutów (5%), które można leczyć objawowo. Objawy te są przemijające i zwykle ustępują w ciągu jednego do dwóch tygodni. W pojedynczych przypadkach wystąpiło zaostrzenie objawów choroby, objawiające się niedrożnością cewki moczowej lub uciskiem (kompresją) rdzenia kręgowego, związaną z obecnością przerzutów. Dlatego pacjentów z przerzutami do kręgosłupa i (lub) niedrożnością górnego lub dolnego odcinka dróg moczowych należy ściśle obserwować w pierwszych tygodniach terapii. Stosowanie analogów GnRH w terapii raka gruczołu krokowego może wiązać się ze zwiększoną utratą masy kostnej i może prowadzić do osteoporozy oraz zwiększonego ryzyka złamań kości. U pacjentów otrzymujących długotrwałe leczenie analogiem GnRH w połączeniu z radioterapią może wystąpić więcej działań niepożądanych, głównie żołądkowo-jelitowych i związanych z radioterapią. **Podmiot odpowiedzialny:** Ipsen Pharma, 65 Quai Georges Gorse, 92100, Boulogne Billancourt, Francja. **Informacji o leku udziela:** Ipsen Poland Sp. z o.o., ul. Chmielna 73, 00-801 Warszawa, tel.: (22) 653 68 00, fax: (22) 653 68 22. **Numer pozwolenia na dopuszczenie do obrotu wydanego przez MZ:** 8944. Kategoria dostępności: Produkt leczniczy wydawany z przepisu lekarza - Rp. 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*W retrospektywnej analizie oceniającej skuteczność tryptoreliny u pacjentów z rakiem stercza udowodniono, że ta forma leczenia pozwala uzyskać poziom kastracyjny testosteronu (<20 ng/dl) u 95% pacjentów. Poziom dla formy 3-miesięcznej oznaczony w dniu 169[1]

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Acknowledgement to Reviewers

The Editorial team of the Central European Journal of Urology takes this opportunity to address and reflect upon the work of all of our reviewers.

In last year our article reviewers have been kind enough to devote their knowledge, experience, and time to work hard and selflessly in order to assist the Authors who have been publishing their works in CEJU further improve their science, skills, and art. Moreover, thanks to their invaluable contribution, our readers have been provided with a full range of high quality, masterly edited articles. Their invaluable contribution is and will be remembered, treasured, and met with admiration and gratitude.

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From among all of the reviewers working for the Central European Journal of Urology, I would like to particularly distinguish those whose contribution to the reviewing process was the greatest. Their commitment, willingness to work, and their kindness to the authors should be an example to all of us.

Bartosz Dybowski

Eugenio Bologna

Ewa Bres-Niewada

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CI – przedział ufności; HR – współczynnik ryzyka; mOS – mediana przeżycia całkowitego; PD-1 – inhibitor receptora programowanej śmierci komórki 1 ; PD-L1 – inhibitor ligandu programowanej śmierci komórki 1

Referencje: 1. Charakterystyka produktu leczniczego Padcev. **2.** Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotinin in previously treated advanced urothelial carcinoma. N Engl J Med. 2021;384(12):1125–1135.

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Informacja o leku

▼ Niniejszy produkt leczniczy będzie dodatkowo monitorowany. Umożliwi to szybkie zidentyfikowanie nowych informacji o bezpieczeństwie. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane. Aby dowiedzieć się, jak zgłaszać działania niepożądane - patrz punkt 4.8. Charakterystyki Produktu Leczniczego (ChPL). **Nazwa produktu leczniczego:** Padcev 20 mg proszek do sporządzania koncentratu roztworu do infuzji, Padcev 30 mg proszek do sporządzania koncentratu roztworu do infuzji. **Skład jakościowy i ilościowy:** Jedna fiolka proszku do sporządzania koncentratu roztworu do infuzji zawiera 20 mg enfortumabu wedotyny (Padcev 20 mg) albo 30 mg enfortumabu wedotyny (Padcev 30 mg). Po rekonstytucji każdy ml roztworu zawiera 10 mg enfortumabu wedotyny. Enfortumab wedotyny składa się z w pełni ludzkiego przeciwciała IgG1 kappa, sprzężonego ze środkiem niszczącym mikrotubule, monometylo aurystatyną E (ang. Monomethyl Auristatin E, MMAE) za pośrednictwem maleimidokaproilo walino-cytrulinowego łącznika rozszczepianego przez proteazę. Pełny wykaz substancji pomocniczych, patrz punkt 6.1. ChPL. **Postać farmaceutyczna:** Proszek do sporządzania koncentratu roztworu do infuzji. **Wskazania do stosowania:** Produkt leczniczy Padcev jest wskazany w monoterapii raka urotelialnego miejscowo zaawansowanego lub z przerzutami u dorosłych pacjentów, którzy otrzymali wcześniej chemioterapię opartą na pochodnych platyny i inhibitor receptora programowanej śmierci komórki 1 lub inhibitor ligandu programowanej śmierci komórki 1 (patrz punkt 5.1 ChPL). **Dawkowanie i sposób podawania:** Leczenie produktem leczniczym Padcev powinien rozpoczął i nadzorował lekarz mający doświadczenie w stosowaniu terapii przeciwnowotworowych. Przed rozpoczęciem leczenia należy zapewnić dobry dostęp żylny (patrz punkt 4.4 ChPL). Dawkowanie: Zalecana dawka enfortumabu wedotyny wynosi 1,25 mg/kg mc. (maksymalnie do 125 mg u pacjentów o masie ciała ≥100 kg) i podaje się ją we wlewie dożylnym przez 30 minut w 1., 8. i 15. dniu 28-dniowego cyklu do czasu progresji choroby lub wystąpienia niemożliwych do zaakceptowania objawów toksyczności. Zalecane zmniejszenie dawki w przypadku działań niepożądanych znajduje się w poniższej tabeli (Tabela 1):

	Stopień zmniejszenia dawki
Dawka początkowa	1,25 mg/kg mc. do 125 mg
Pierwsze zmniejszenie dawki	1,0 mg/kg mc. do 100 mg
Drugie zmniejszenie dawki	0,75 mg/kg mc. do 75 mg
Trzecie zmniejszenie dawki	0,5 mg/kg mc. do 50 mg

Modyfikacje dawki: Informacja o przerwaniu, zmniejszeniu i odstawieniu dawki u pacjentów z rakiem urotelialnym miejscowo zaawansowanym lub z przerzutami znajduje się w poniższej tabeli (Tabela 2):

Działanie niepożądane	**Nasilenie***	**Modyfikacja dawki***
Reakcje skórne	Podejrzewany zespół Stevensa-Johnsona (ang. Stevens-Johnson Syndrome, SJS) lub martwica toksyczno-rozpływna naskórka (ang. Toxic Epidermal Necrolysis, TEN), lub zmiany pęcherzowe	Natychmiast wstrzymać podawanie i objąć pacjenta opieką specjalistyczną.
	Potwierdzony SJS lub TEN; stopień 4. lub nawracający stopień 3.	Zakończyć leczenie
	Pogorszenie stopnia 2. Stopień 2. z gorączką Stopień 3.	□ Wstrzymać podawanie do uzyskania stopnia ≤1. □ Rozważyć objęcie pacjenta opieką specjalistyczną □ Wznowić podawanie w tej samej dawce lub rozważyć zmniejszenie dawki o jeden stopień (patrz Tabela 1)
Hiperglikemia	Glikemia >13,9 mmol/l (>250 mg/dl)	□ Wstrzymać podawanie, dopóki zwiększone stężenie glukozy nie zmniejszy się do wartości ≤13,9 mmol/l (≤250 mg/dl) □ Wznowić leczenie w tej samej dawce
Nieinfekcyjne zapalenie płuc/ śródmiąższowa choroba płuc (ang. interstitial lung disease, ILD)	Stopień 2.	Wstrzymać podawanie do uzyskania stopnia ≤1., następnie wznowić podawanie w tej samej dawce lub rozważyć zmniejszenie dawki o jeden stopień (patrz Tabela 1)
	Stopień ≥3.	Zakończyć leczenie
Neuropatia obwodowa	Stopień 2.	□ Wstrzymać podawanie do uzyskania stopnia ≤1. □ W przypadku pierwszego wystąpienia wznowić leczenie w tej samej dawce □ W przypadku nawrotu wstrzymać podawanie do uzyskania stopnia ≤1., a następnie wznowić leczenie w dawce zmniejszonej o jeden stopień (patrz Tabela 1)
	Stopień ≥3.	Zakończyć leczenie

*Toksyczności oceniano według Wspólnych Kryteriów Terminologii Zdarzeń Niepożądanych National Cancer Institute (ang. National Cancer Institute Common Terminology Criteria for Adverse Events; NCI-CTCA), wersja 5,0, zgodnie z którymi stopień 1. oznacza nasilenie łagodne, stopień 2. umiarkowane, stopień 3. ciężkie, a stopień 4. zagrażające życiu. Specjalne grupy pacjentów: Osoby starsze - Nie ma konieczności dostosowania dawki u pacjentów w wieku ≥65 lat (patrz punkt 5.2 ChPL). Zaburzenia czynności nerek: Nie ma konieczności dostosowania dawki u pacjentów z łagodnymi [klirens kreatyniny (ang. Creatinine Clearance, CrCL) >60–90 ml/min], umiarkowanymi (CrCL 30–60 ml/min) ani ciężkimi (CrCL 15–<30 ml/min) zaburzeniami czynności nerek. Enfortumabu wedotyny nie oceniano u pacjentów ze schyłkową niewydolnością nerek (CrCL <15 ml/min) (patrz punkt 5.2 ChPL). Zaburzenia czynności wątroby: Nie ma konieczności dostosowania dawki u pacjentów z łagodnymi zaburzeniami czynności wątroby [bilirubina całkowita od 1 do 1,5 × górnej granicy normy (GGN) i dowolna aktywność aminotransferazy asparaginianowej (AST) lub bilirubina całkowita ≤GGN i AST >GGN]. Enfortumab wedotyny oceniano tylko w ograniczonej grupie pacjentów z umiarkowanymi zaburzeniami czynności wątroby, natomiast nie oceniano go u pacjentów z ciężkimi zaburzeniami czynności wątroby (patrz punkt 5.2 ChPL). Dzieci i młodzież: Enfortumab wedotyny nie ma zastosowania u dzieci i młodzieży w leczeniu raka urotelialnego miejscowo zaawansowanego lub z przerzutami. Sposób podawania: Produkt leczniczy Padcev podaje się dożylnie. Zalecana dawka musi być podawana we wlewie dożylnym przez 30 minut. Enfortumabu wedotyny nie można podawać we wstrzyknięciu dożylnym ani w szybkim wstrzyknięciu dożylnym (bolus). Instrukcja dotycząca rekonstytucji i rozcieńczenia produktu leczniczego przed podaniem, patrz punkt 6.6.ChPL. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą wymienioną w punkcie 6.1. ChPL. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** Identyfikowalność: W celu poprawienia identyfikowalności biologicznych produktów leczniczych należy dokładnie odnotować nazwę i numer serii podawanego produktu; Reakcje skórne: Reakcje skórne związane z podawaniem enfortumabu wedotyny są wynikiem jego wiązania do nektyny-4 ulegającej ekspresji w skórze. W przypadku wystąpienia gorączki lub objawów grypopodobnych, które mogą być pierwszymi objawami ciężkiej reakcji skórnej, należy obserwować pacjentów; Donoszono o występowaniu reakcji skórnych o nasileniu łagodnym do umiarkowanego, głównie w postaci wysypki plamisto-grudkowej (patrz punkt 4.8 ChPL). U pacjentów leczonych enfortumabem wedotyny występowały również skórne działania niepożądane o ciężkim nasileniu, w tym SJS i TEN, ze skutkiem śmiertelnym, głównie w trakcie pierwszego cyklu leczenia. W badaniach klinicznych mediana czasu do wystąpienia reakcji skórnych o ciężkim nasileniu wynosiła 0,6 miesiąca (zakres od 0,1 do 6,4). Należy monitorować pacjentów w kierunku reakcji skórnych, począwszy od pierwszego cyklu i przez cały czas leczenia. W przypadku wystąpienia reakcji skórnych o nasileniu łagodnym do umiarkowanego można rozważyć odpowiednie leczenie, takie jak miejscowe podawanie kortykosteroidów i podawanie leków przeciwhistaminowych. W razie podejrzenia SJS lub TEN, lub w przypadku wystąpienia zmian pęcherzowych należy natychmiast wstrzymać leczenie i objąć pacjentów opieką specjalistyczną; potwierdzenie histologiczne, w tym rozważenie wykonania kilku biopsji, ma kluczowe znaczenie dla wczesnego rozpoznania, ponieważ diagnoza i interwencja mogą poprawić rokowanie. Należy trwale odstawić produkt leczniczy Padcev w przypadku potwierdzenia SJS lub TEN, reakcji stopnia 4. lub nawracających ciężkich reakcji skórnych. W przypadku pogorszenia reakcji stopnia 2., wystąpienia reakcji stopnia 2. z gorączką lub wystąpienia reakcji skórnych stopnia 3. należy wstrzymać leczenie do uzyskania stopnia ≤1. i rozważyć objęcie pacjentów opieką specjalistyczną. Wznowić leczenie w tej samej dawce lub rozważyć zmniejszenie dawki o jeden stopień (patrz punkt 4.2 ChPL); Nieinfekcyjne zapalenie płuc/ILD: U pacjentów leczonych enfortumabem wedotyny występowały nieinfekcyjne zapalenie płuc/ILD o ciężkim nasileniu, zagrażające życiu lub prowadzące do zgonu (patrz punkt 4.8 ChPL). Pacjentów należy monitorować w kierunku przedmiotowych i podmiotowych objawów nieinfekcyjnego zapalenia płuc/ILD, takich jak niedotlenienie, kaszel, duszność lub nacieki śródmiąższowe w badaniach radiologicznych. W przypadku zdarzeń stopnia ≥ 2. należy podać kortykosteroidy (np. prednizon lub jego odpowiednik w dawce początkowej 1-2 mg/kg mc./dobę, którą następnie należy stopniowo zmniejszać). Należy wstrzymać leczenie produktem leczniczym Padcev w przypadku nieinfekcyjnego zapalenia płuc/ILD stopnia 2. i rozważyć zmniejszenie dawki. Należy zakończyć leczenie produktem leczniczym Padcev w przypadku nieinfekcyjnego zapalenia płuc/ILD stopnia ≥3. (patrz punkt 4.2 ChPL); Hiperglikemia: Hiperglikemia i kwasica ketonowa cukrzycowa (ang. Diabetic Ketoacidosis, DKA), w tym przypadki zgonów, występowały u pacjentów z cukrzycą w wywiadzie lub bez niej, leczonych enfortumabem wedotyny (patrz punkt 4.8 ChPL). Hiperglikemia występowała częściej u pacjentów z wcześniej istniejącą hiperglikemią lub wysokim wskaźnikiem masy ciała (BMI ≥30 kg/m^2). Pacjentów ze stężeniem HbA1c ≥8% w punkcie wyjściowym wykluczono z badań klinicznych. Przed podaniem dawki i okresowo przez cały czas trwania leczenia zgodnie ze wskazaniami klinicznymi należy monitorować stężenie glukozy u pacjentów z cukrzycą lub narażonych na ryzyko cukrzycy bądź hiperglikemii. Jeżeli stężenie glukozy jest podwyższone, tj. ma wartość >13,9 mmol/l (>250 mg/dl), należy odstawić produkt leczniczy Padcev do czasu aż stężenie glukozy nie zmniejszy się do wartości ≤13,9 mmol/l (≤250 mg/dl) i wdrożyć odpowiednie leczenie (patrz punkt 4.2 ChPL); Neuropatia obwodowa: Podczas podawania enfortumabu wedotyny występowała neuropatia obwodowa, głównie neuropatia obwodowa czuciowa, w tym reakcje stopnia ≥3. (patrz punkt 4.8 ChPL). Pacjentów z wcześniej istniejącą neuropatią obwodową stopnia ≥2. wykluczono z badań klinicznych. Pacjentów należy monitorować w kierunku wystąpienia objawów lub nasilenia istniejącej neuropatii obwodowej, ponieważ tacy pacjenci mogą wymagać opóźnienia w podawaniu, zmniejszenia dawki lub odstawienia enfortumabu wedotyny (patrz Tabela 1). Produkt leczniczy Padcev należy trwale odstawić w przypadku neuropatii obwodowej stopnia ≥3. (patrz punkt 4.2 ChPL); Zaburzenia oka: U pacjentów leczonych enfortumabem wedotyny występowały zaburzenia oka, głównie zespół suchego oka (patrz punkt 4.8 ChPL). Należy monitorować pacjentów w kierunku zaburzenia oka. W ramach profilaktyki zespołu suchego oka należy rozważyć podawanie sztucznych łez i skierowanie na badanie okulistyczne, jeżeli objawy oczne nie ustąpiły lub uległy pogorszeniu. Wynaczynienie w miejscu podania wlewu: W przypadku wynaczynienia obserwowano uszkodzenie skóry i tkanek miękkich po podaniu enfortumabu wedotyny (patrz punkt 4.8 ChPL). Przed rozpoczęciem podawania produktu leczniczego Padcev należy zapewnić dobry dostęp żylny i w trakcie podawania monitorować możliwe wynaczynienia w miejscu podania wlewu. Jeżeli nastąpi wynaczynienie, należy przerwać wlew i monitorować pacjenta w kierunku wystąpienia działań niepożądanych. Toksyczność dla zarodka lub płodu i antykoncepcja: Kobiety w ciąży należy poinformować o potencjalnym ryzyku dla płodu (patrz punkty 4.6 i 5.3 ChPL). Kobietom w wieku rozrodczym należy zalecić wykonanie testu ciążowego w ciągu 7 dni przed rozpoczęciem leczenia enfortumabem wedotyny, stosowanie skutecznej metody antykoncepcji w trakcie leczenia i przez co najmniej 12 miesięcy od zakończenia leczenia. Zaleca się, aby mężczyźni leczeni enfortumabem wedotyny nie spłodzili dziecka w czasie trwania leczenia i przez okres do 9 miesięcy od podania ostatniej dawki produktu leczniczego Padcev. **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa: Najczęstszymi działaniami niepożądanymi enfortumabu wedotyny były łysienie (48,8%), zmęczenie (46,8%), zmniejszony apetyt (44,9%), neuropatia obwodowa czuciowa (38,7%), biegunka (37,6%), nudności (36%), świąd (33,4%), zaburzenia smaku (29,9%), niedokrwistość (26,5%), zmniejszenie masy ciała (23,4%), wysypka plamisto-grudkowa (22,9%), suchość skóry (21,6%), wymioty (18,4%), zwiększona aktywność aminotransferazy asparaginianowej (15,3%), hiperglikemia, (13,1%), zespół suchego oka (12,8%), zwiększona aktywność aminotransferazy alaninowej (12,1%) i wysypka (10,4%).Najczęstszymi ciężkimi działaniami niepożądanymi były biegunka (2%) i hiperglikemia (2%). Dziewięć procent pacjentów trwale odstawiło enfortumab wedotyny z powodu działań niepożądanych; najczęstszym działaniem niepożądanym (≥2%) prowadzącym do odstawienia dawki była neuropatia obwodowa czuciowa (4%). Działania niepożądane prowadzące do przerwania podawania dawki wystąpiły u 44% pacjentów; najczęstszymi działaniami niepożądanymi (≥2%) prowadzącymi do przerwania podawania dawki były: neuropatia obwodowa czuciowa (15%), zmęczenie (7%), wysypka plamisto-grudkowa (4%), zwiększenie aktywności aminotransferazy asparaginianowej (4%), zwiększenie aktywności aminotransferazy alaninowej (4%), niedokrwistość (3%), biegunka (3%) i hiperglikemia (3%). Trzydzieści pięć procent pacjentów wymagało zmniejszenia dawki z powodu wystąpienia działań niepożądanych; najczęstszymi działaniami niepożądanymi (≥2%) prowadzącymi do zmniejszenia dawki były: neuropatia obwodowa czuciowa (10%), zmęczenie (5%), wysypka plamisto-grudkowa (4%) i zmniejszony apetyt (2%). Bezpieczeństwo stosowania enfortumabu wedotyny w monoterapii oceniano u 680 pacjentów z rakiem urotelialnym miejscowo zaawansowanym lub z przerzutami, którzy w badaniach klinicznych otrzymali dawkę 1,25 mg/kg mc. w 1., 8. i 15. dniu 28-dniowego cyklu (patrz tabela 3). Mediana czasu narażenia pacjentów na enfortumab wedotyny wynosiła 4,7 miesiąca (zakres od 0,3 do 34,8 miesiąca). Działania niepożądane obserwowane podczas badań klinicznych wymieniono w tym punkcie według częstości występowania. Częstość określono w następujący sposób: bardzo często (≥1/10); często (≥1/100 do <1/10); niezbyt często (≥1/1 000 do <1/100); rzadko (≥1/10 000 do <1/1 000); bardzo rzadko (<1/10 000); częstość nieznana (częstość nie może być określona na podstawie dostępnych danych). W obrębie każdej grupy o określonej częstości występowania objawy niepożądane są wymienione zgodnie ze zmniejszającą się ciężkością. **Zaburzenia krwi i układu chłonnego:** Bardzo często: niedokrwistość; Nieznana[1]: neutropenia, gorączka neutropeniczna, zmniejszona liczba neutrofili; **Zaburzenia metabolizmu i odżywiania:** Bardzo często: Hiperglikemia, zmniejszony apetyt; **Zaburzenia układu nerwowego:** Bardzo często: neuropatia obwodowa czuciowa, zaburzenia smaku; Często: neuropatia obwodowa, neuropatia obwodowa ruchowa, neuropatia obwodowa czuciowo-ruchowa, parestezja, niedoczulica, zaburzenia chodu, osłabienie mięśni; Niezbyt często: Polineuropatia demielinizacyjna, polineuropatia, neurotoksyczność, dysfunkcja ruchowa, zaburzenia czucia, atrofia mięśni, neuralgia, porażenie nerwu strzałkowego, utrata czucia, uczucie pieczenia skóry, uczucie pieczenia; **Zaburzenia oka:** Bardzo często: Zespół suchego oka; **Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia:** Często: nieinfekcyjne zapalenie płuc; Niezbyt często: śródmiąższowa choroba płuc; **Zaburzenia żołądka i jelit:** Bardzo często: biegunka, wymioty, nudności; **Zaburzenia skóry i tkanki podskórnej:** Bardzo często: łysienie, świąd, wysypka, wysypka plamisto-grudkowa, suchość skóry; Często: wykwit polekowy, złuszczanie skóry, zapalenie spojówek, dermatoza pęcherzowa, powstawanie pęcherzy, zapalenie jamy ustnej, zespół erytrodystezji dłoniowo-podeszwowej, wyprysk, rumień, wysypka rumieniowata, wysypka plamista, wysypka grudkowa, wysypka świądowa, wysypka pęcherzykowa; Niezbyt często: uogólnione złuszczające zapalenie skóry, rumień wielopostaciowy, wysypka złuszczająca, pemfigoid, wysypka plamisto-pęcherzykowa, zapalenie skóry, alergiczne zapalenie skóry, kontaktowe zapalenie skóry, wyprzenie, podrażnienie skóry, wyprysk zastoinowy, pęcherz z krwią; Nieznana[1]: Martwica toksyczno-rozpływna naskórka, zespół Stevensa-Johnsona, martwica naskórka, związane z lekiem symetryczne wyprzenie i wykwity zgięciowe. **Zaburzenia ogólne i stany w miejscu podania:** Bardzo często: zmęczenie; Często: Wynaczynienie w miejscu wlewu; **Badania diagnostyczne:** Bardzo często: zwiększona aktywność aminotransferazy alaninowej, zwiększona aktywność aminotransferazy asparaginianowej, zmniejszona masa ciała; [1]Na podstawie danych zgromadzonych na całym świecie po wprowadzeniu produktu do obrotu. Opis wybranych działań niepożądanych: Immunogenność: Łącznie 590 pacjentów zbadano w kierunku immunogenności enfortumabu wedotyny podanego w dawce 1,25 mg/kg mc.; 15 pacjentów potwierdzono jako dodatnich pod względem obecności przeciwciał przeciwlekowych (ang. Anti Drug Antibodies, ADA) w punkcie wyjściowym, a spośród pacjentów ujemnych w punkcie wyjściowym (N = 575), łącznie 16 (2,8%) było później dodatnich (13 przejściowo i 3 trwale). Ze względu na ograniczoną liczbę pacjentów, u których potwierdzono obecność przeciwciał przeciwko produktowi leczniczemu Padcev, nie można wyciągnąć wniosków dotyczących możliwego wpływu immunogenności na skuteczność, bezpieczeństwo stosowania i farmakokinetykę produktu. Reakcje skórne: W badaniach klinicznych reakcje skórne wystąpiły u 55% (375) spośród 680 pacjentów leczonych enfortumabem wedotyny w dawce 1,25 mg/kg mc. Reakcje skórne o ciężkim nasileniu (stopień 3. lub 4.) wystąpiły u 13% (85) pacjentów i większość z tych reakcji obejmowała wysypkę plamisto-grudkową, wysypkę rumieniowatą, wysypkę lub wykwit polekowy. Mediana czasu do wystąpienia reakcji skórnych o ciężkim nasileniu wynosiła 0,62 miesiąca (zakres od 0,1 do 6,4 miesiąca). Ciężkie reakcje skórne wystąpiły u 3,8% (26) pacjentów. W badaniu klinicznym EV-201 (N = 214) wśród pacjentów, u których wystąpiły reakcje skórne u 75% objawy ustąpiły całkowicie, a u 14% uzyskano częściową poprawę (patrz punkt 4.4 ChPL). Nieinfekcyjne zapalenie płuc/ILD: W badaniach klinicznych nieinfekcyjne zapalenie płuc wystąpiło u 15 (2,2%), a ILD u 2 (0,3%) spośród 680 pacjentów leczonych enfortumabem wedotyny w dawce 1,25 mg/kg mc. Mniej niż 1% pacjentów doświadczyło ciężkiego (stopień 3.–4.) nieinfekcyjnego zapalenia płuc lub ILD. Nieinfekcyjne zapalenie płuc lub ILD doprowadziły do przerwania leczenia enfortumabem wedotyny odpowiednio u 0,1% i 0,3% pacjentów. Nie było zgonów z powodu ILD ani nieinfekcyjnego zapalenia płuc. Mediana czasu do wystąpienia nieinfekcyjnego zapalenia płuc dowolnego stopnia lub ILD wynosiła 3,6 miesiąca (zakres od 0,8 do 6,0 miesięcy), a mediana czasu trwania wynosiła 1,4 miesiąca (zakres od 0,2 do 27,5 miesiąca). Spośród 17 pacjentów, u których wystąpiło nieinfekcyjne zapalenie płuc lub ILD, u 6 (35,3%) objawy ustąpiły. Hiperglikemia: W badaniach klinicznych hiperglikemia (stężenie glukozy we krwi >13,9 mmol/l) wystąpiła u 14% (98) spośród 680 pacjentów leczonych enfortumabem wedotyny w dawce 1,25 mg/kg mc. Ciężkie zdarzenia hiperglikemii wystąpiły u 2,2% pacjentów, u 7% pacjentów wystąpiła ciężka (stopień 3.–4.) hiperglikemia, a u 0,3% pacjentów nastąpił zgon, u jednego pacjenta hiperglikemia a u drugiego kwasica ketonowa cukrzycowa. Częstość występowania hiperglikemii stopnia 3.–4. systematycznie rosła u pacjentów z wyższym wskaźnikiem masy ciała i u pacjentów z większym stężeniem hemoglobiny A1C (HbA1c) w punkcie wyjściowym. Mediana czasu do wystąpienia hiperglikemii wynosiła 0,6 miesiąca (zakres od 0,1 do 20,3). W badaniu klinicznym EV-201 (N = 214) w czasie ostatniej oceny u 61% pacjentów objawy ustąpiły całkowicie, a u 19% pacjentów nastąpiła częściowa poprawa (patrz punkt 4.4 ChPL). Neuropatia obwodowa: W badaniach klinicznych neuropatia obwodowa wystąpiła u 52% (352) spośród 680 pacjentów leczonych enfortumabem wedotyny w dawce 1,25 mg/kg mc. Cztery procent pacjentów doświadczyło ciężkiej (stopień 3.–4.) neuropatii obwodowej, w tym zdarzeń czuciowych i ruchowych. Mediana czasu do wystąpienia stopnia ≥2. wynosiła 4,6 miesiąca (zakres od 0,1 do 15,8). W badaniu klinicznym EV-201 (N = 214) w czasie ostatniej oceny, u 19% pacjentów objawy ustąpiły całkowicie, a u 39% pacjentów nastąpiła częściowa poprawa (patrz punkt 4.4 ChPL). Zaburzenia oka: W badaniach klinicznych 30% pacjentów miało zespół suchego oka w trakcie leczenia enfortumabem wedotyny w dawce 1,25 mg/kg mc. Leczenie przerwało 1,3% pacjentów, a 0,1% trwale przerwało leczenie z powodu zespołu suchego oka. Ciężki (stopnia 3.) zespół suchego oka wystąpił jedynie u 3 pacjentów (0,4%). Mediana czasu do wystąpienia zespołu suchego oka wynosiła 1,7 miesiąca (zakres od 0 do 19,1 miesiąca) (patrz punkt 4.4 ChPL). **Zgłaszanie podejrzewanych działań niepożądanych:** Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, Al. Jerozolimskie 181C, PL-02 222 Warszawa, tel.: +48 22 4921 301, faks: +48 22 4921 309; Strona internetowa: https://smz.ezdrowie.gov.pl; **Podmiot odpowiedzialny:** Astellas Pharma Europe B.V., Sylviusweg 62, 2333 BE Leiden, Holandia. **Numery pozwoleń na dopuszczenie do obrotu:** EU/1/21/1615/001-002 - wydane przez Komisję Europejską. **Kategoria dostępności:** Produkt leczniczy wydawany na receptę do zastrzeżonego stosowania - Rpz.

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EDITORIAL

The impact of artificial intelligence in revolutionizing all aspects of urological care: a glimpse in the future

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Key Words: AI ‹› artificial intelligence ‹› urology ‹› machine learning ‹› quality of life ‹› patient outcomes

There has been a technological revolution in the field of urology over the last 2 decades. A part of this advancement is the advent of artificial intelligence (AI), which is growing exponentially and has the potential to perform complex tasks, analyse data by emulating human cognitive function and revolutionise patient care [1, 2].

AI has a myriad of applications and is leading to a paradigm shift in healthcare industry. Its primary aim in healthcare is to understand and analyse the association between prevention and/or treatment, and related clinical outcomes [3, 4]. The 4 subsets of AI in healthcare are machine learning, natural language processing, deep learning and artificial neural networks, and computer vision. AI methodologies seem to be more precise in prediction and for studying big data than traditional statistics and is therefore widely used in urology. It has led to evidence-based and personalised treatment by having patient data available to urologists.

The role of AI expands to various benign and malignant conditions such as urolithiasis, benign prostate enlargement (BPH), paediatric urology, renal transplant, urogynaecology, robotic surgery, and uro-oncology pertaining to prostate, kidney, bladder and prostate [5–8]. Our editorial reviews the broad role of AI in urology for diagnosis and risk assessment, treatment planning and precision medicine, robotic surgery and AI-assisted procedures, improved patient care and outcomes, challenges and ethical considerations, and its future role within urology [9, 10, 11].

Diagnosis and risk assessment

Early diagnosis and risk assessment with AI-driven algorithms seem to be able to analyse medical imaging of data from USS, CT or MRI with speed and accuracy. This can be seen in prostate cancer detection which can detect subtle imaging abnormalities which can potentially be missed by radiologists. Similarly, by analysing electronic health records and patient data, AI related algorithms can notice patterns which may not be readily recognised by urologists,

and help in correlation with personalised and proactive treatment, improving outcomes [12].

Treatment planning and precision medicine

After the initial diagnosis, AI can help with implementation of precision medicine by tailored and individualised treatment [13]. This can be done by analysing urological history, any genetic information and previous treatments. Herein, AI algorithms can potentially come with best urological plan. For example, in bladder cancer it can help with selection of surgery vs chemotherapy or immunotherapy taking into account drug interactions and potential side effects. This approach can maximise treatment efficacy, reduce complications, and ultimately lead to better outcomes and patient experience.

Robotic surgery and artificial intelligence-assisted procedures

While robotic surgery has been used in urology for over 2 decades, AI has been instrumental in enabling the safety and precision with robotic surgeries. AI allows for image processing and real time feedback which in turn allows for increased accuracy with complex procedures and also translating to better patient outcomes. In addition, it can help with tele training, tele mentoring and tele surgery helping with remote guidance to less experienced trainees and urologists. It therefore allows for distant learning and knowledge sharing with mentoring of urologists.

Improved patient care and outcomes

AI has the ability to transform patient care with the chatbots and virtual assistants that can provide evidence-based information, answer queries and offer advice on urological conditions. The enhances patient participation and involves them in the decision-making process thereby also minimising burden on healthcare providers.

This ability of AI can really help with chronic conditions such as BPH, urinary incontinence and kidney stone disease [14]. This aspect of AI can be helped with wearable devices and can allow for early intervention and individualised treatment. This might even have improved outcomes for such patients [15, 16].

Challenges and ethical considerations and future of artificial intelligence

As AI gets integrated into mainstream urology, care must be taken to address the ethical and legal challenges [17]. Data security and privacy along with AI algorithms adhering to strict guidelines and regulations are a must for responsible AI and in protecting patient confidentiality [18]. Similarly, steps must be taken to avoid AI hallucinations and data bias and ensuring that the technological innovations are available to all irrespective of their socio-economic status. The cost of data storing and processing, legal aspects, decision making in difficult scenarios, risk management, potential job losses especially for the newer generation of medical students are other challenges which can affect its future potential and usage. But its use as an alternate to the google search engine can also be a good alternate source of information for patients and clinicians alike.

The future of urology and AI are inter-linked and with continued evolvement, we will see more potential avenues of its use and clinical applications and perhaps it is time for guidelines to also adopt this [19].

CONCLUSIONS

AI has already transformed the journey of urological patients and healthcare providers and is shaping the present and future of urological landscape. Urology needs to embrace AI for to harness its capability and improve patient care, yet care must be taken to ensure that the ethical, legal and social challenges are addressed for a better patient experience and improved quality of life.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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REVIEW PAPER

UROLOGICAL ONCOLOGY

The use of indocyanine green in partial nephrectomy: a systematic review

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Introduction The aim of this review was to assess the outcomes of partial nephrectomy using indocyanine green (ICG) regarding ischemia time, positive surgical margins (PSM), estimated blood loss (EBL) and estimated GFR reduction while also suggesting the optimal dosage scheme.

Material and methods A systematic review was performed using Medline (PubMed), ClinicalTrials.gov, and Cochrane Library (CENTRAL) databases, in concordance with the PRISMA statement. Studies in English regarding the use of indocyanine green in partial nephrectomy were reviewed. Reviews and meta-analyses, editorials, perspectives, and letters to the editors were excluded.

Results Individual ICG dose was 5 mg in most of the studies. The mean warm ischemia time (WIT) on each study ranged from 11.6 minutes to 27.2 minutes. The reported eGFR reduction ranged from 0% to 15.47%. Lowest mean EBL rate was 48.2 ml and the highest was 347 ml. Positive surgical margin rates were between 0.3% to 11%.

Conclusions Indocyanine green seems to be a useful tool in partial nephrectomy as it can assist surgeons in identifying tumor and its related vasculature. Thereby, warm ischemia time can be reduced and, in some cases, selective ischemia can be implemented leading to better renal functional preservation.

Key Words: partial nephrectomy ‹› indocyanine green ‹› ICG ‹› Near-infrared fluorescence ‹› NIRF ‹› renal cancer

INTRODUCTION

Identification of the tumor and its related vasculature while being in the operating room and renal functional preservation are paramount elements in kidney surgery, affecting the surgeon's results and patients' quality of life. Partial nephrectomy (PN) has been established as the preferred treatment for small renal masses, as it offers greater renal functional preservation and oncological equivalence with radical nephrectomy [1–4]. Preoperative imaging and intraoperative ultrasonography are used by most surgeons for tumor localization and identification of anatomical structures on patients undergoing PN. However, despite these advancements there is still room for improvement in accurately identifying tumors and vasculature. Near-infrared fluorescence (NIRF) using indocyanine green (ICG) has been adopted to enhance the surgeon's ability to reduce ischemia time or even obtain selective ischemia limited only to the tumor and immediate adjacent normal parenchyma, leaving blood flow to the remainder tissue uninterrupted during surgery. ICG received approval from the Food and Drug Administration (FDA) in 1959 for clinical use and has since been commonly utilized in a broad range of medical procedures such as

cholangiography, gastrointestinal surgeries and lymph node dissections due to its impressive pharmacokinetic properties [5]. This systematic review aims to assess the outcomes of PN using ICG regarding ischemia time, positive surgical margins (PSM), estimated blood loss (EBL) and estimated GFR reduction while also suggesting the optimal dosage scheme.

MATERIAL AND METHODS

This systematic review was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [6]. Bibliographic search was performed in Medline (PubMed), ClinicalTrials.gov, and Cochrane Library (CENTRAL) from database inception until March 1, 2023. The following medical subject heading terms were used in combination with Boolean operators: indocyanine green, fluorescence, nephrectomy. Two independent reviewers (S.K., T.B.) screened all articles retrieved by the initial search. All disagreements were resolved with discussion, and final decision was reached by consensus with a third reviewer (L.T.). Reference lists were systematically searched for potentially eligible, missed studies. The protocol was registered to PROSPERO (CRD42023424430).

Study criteria

Clinical trials, cohort studies, and case-control studies were considered for inclusion. Only well-described studies were included in analysis. In order to be characterized as well-described, a study had to include a documented outcome concerning the intraoperative use of ICG and fulfill at least 5 of the following 6 criteria:

1. research question regarding intraoperative use of ICG on partial nephrectomy
2. individual dosage or dosage range,
3. results regarding surgical margins
4. ischemia time
5. estimated GFR change (eGFR)
6. estimated blood loss (EBL)

Case reports, systematic reviews and metanalyses were excluded. Excluded studies met ≥1 of the following criteria:(1) irrelevant to the subject studies, (2) studies published in a non-English language, (3) reviews and meta-analyses, editorials, perspectives, and letters to the editors, (4) studies fulfilling less than five from the aforementioned inclusion criteria.

Evidence synthesis

Literature search revealed 522 studies from which 437 were excluded after abstract screening and/or duplicate removal. After reviewing full-text, 70 records did not meet our criteria and were therefore excluded. Finally, 14 studies were deemed eligible for qualitative analysis [7–20]. The flow diagram is shown in Figure 1. Table 1 shows general characteristics of all articles included in our review. We saw greater utility in organizing our discussion in a systematic review form without meta-analysis, to avoid biased numerical conclusions due to the small sample sizes and to present the variety of surgical experiences obtained through synthetic logical interrelations. Hozo et al. [21] and Wan et al. [22] formulas were used to transform median and interquartile ranges to mean and standard deviation, wherever necessary in order to interpret better each study.

Risk of bias assessment

Risk of bias assessment was performed by two authors (S.K and L.T) using the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for nonrandomized studies [23] (see Table 2). Most common reasons for the studies to be classified as having moderate or serious risk of bias was the selection bias during participant

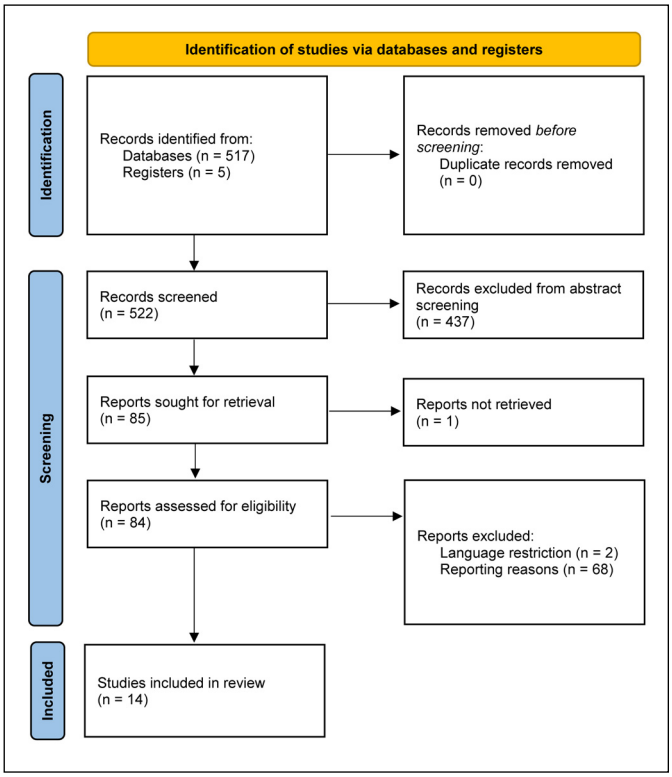

Figure 1. *Review flow diagram based on PRISMA 2020 for new systematic reviews which included searches of databases and registers only.*

Table 1. *Baseline characteristic*

Study	Sample size	Age mean (years)	Type of ischemia	Type of appoach	Tumor complexity	Tumor size	Control group	Follow-up (days)
Tobis et al. (2011) [7] Prospective, USA	11	61	Global ischemia	Robot assisted: 11/11	Median RENAL score: 7.5	Median radiographic lesion: 3.6 cm	NA	NA
Borofsky et al. (2012) [8] Prospective, USA	34	60.1	Selective ischemia	Robot assisted: 34/34	Median RENAL score: 8	Mean tumor size: 2.79 cm	Retrospective Matched-pair analysis: 27 patients	13.5
Krane et al. (2012) [9] Prospective, USA	47	59.6	Global ischemia	Robot assisted: 47/47	Median RENAL score: 6	Median tumour size: 2.7 cm	Retrospective group:47 patients	150
Angell et al. (2013) [10] Retrospective, USA	79	55	Global ischemia	Robot assisted: 79/79	Mean RENAL score: 8	Mean tumor size: 3.5 cm	NA	NA
Harke et al. (2013) [11] Retrospective, Germany	22	62.8	Selective ischemia	Robot assisted: 22/22	Mean RENAL score: 8.1	Mean tumor size: 3.77 cm	Retrospective Matched-pair analysis: 15 patients	NA
Bjurlin et al. (2014) [12] Retrospective, USA	70	56.3	Selective ischemia	Robot assisted: 70/70	Median RENAL score: 6	Median tumor size: 2.6 cm	NA	14
Lanchon et al. (2018) [13] Prospective, France	30	65.3	Selective ischemia	Robot assisted: 30/30	NA	Median tumor size: 3 cm	Retrospective Matched-pair analysis: 25 patients	180
Simone et al. (2018) [14] Prospective, Italy	10	61.3	Selective ischemia	Robot assisted: 10/10	Median RENAL score: 9	Median tumor size: 3 cm	NA	360
Mattevi et al. (2018) [15] Prospective, Italy	20	65.3	Selective ischemia	Robot assisted: 20/20	NA	Median tumor size: 4 cm	42 patients who underwent selective clamping RAPN	30
Diana et al. (2020) [16] Retrospective, Italy	318	61.1	Mixed approach	Robot assisted: 318/318	RENAL score categories: Low: 36.5% Intermediate: 51.9% High: 11.6%	Median tumor size: 3 cm	NA	NA
Gadus et al. (2020) [17] Retrospective, Czech Republic	37	57	Mixed approach	Robot assisted: 37/37	RENAL score categories: Low: 21% Intermediate: 76% High: 3%	Mean tumor size: 3.1 cm	NA	NA
Sentell et al. (2020) [18] Retrospective, USA	288	57.9	Selective ischemia	Robot assisted: 288/288	Mean RENAL score: 7.3	Mean tumor size: 3.3 cm	NA	NA
Wang et al. (2021) [19] Retrospective, China	21	61.1	Global ischemia	Laparoscopic: 21/21	Mean RENAL score: 7.9	Mean tumor size: 4.4 cm	39 patients laparoscopy without ICG	NA
Yang et al. (2022) [20] Retrospective, China	21	55.6	Global ischemia	Robot assisted: 21/21	Median RENAL score: 8	Median tumor size: 3.5 cm	106 patients RAPN without ICG	180

NA – not available

selection and the inadequate adjustment for confounding factors.

ICG dosage

There is no general consensus for the optimal total dose for ICG administration. Due to the lack of standardization of ICG dosing, the dose and frequency of injections are decided by the surgeon's judgement. However, it is generally accepted that the daily maximum dose should not surpass 2 mg/kg as this is considered a toxic level [7, 9, 11]. Thirteen studies in our review provided information for the dosage scheme followed by the surgeons.

Table 2. *Risk of bias assessment for non-randomized studies*

First author et al. (year)	Confounding	Participant Selection	Intervention classi-fication	Deviation from intended treatment	Missing data	Outcome measure-ment	Selected reporting	Overall bias
Tobis et al. (2011)	Moderate	Serious	Low	Low	Low	Moderate	Low	Serious
Borofsky et al. (2012)	Moderate	Serious	Low	Low	Moderate	Moderate	Low	Serious
Krane et al. (2012)	Moderate	Serious	Low	Low	Moderate	Low	Low	Serious
Angell et al. (2013)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Harke et al. (2013)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Bjurlin et al. (2014)	Moderate	Serious	Low	Low	Low	Moderate	Low	Serious
Lanchon et al. (2018)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Simone et al. (2018)	Low	Low	Low	Low	Low	Low	Low	Low
Mattevi et al. (2018)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Diana et al. (2020)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Gadus et al. (2020)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Sentell et al. (2020)	Moderate	Serious	Low	Low	Low	Moderate	Low	Serious
Wang et al. (2021)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Yang et al. (2022)	Moderate	Serious	Low	Low	Moderate	Low	Low	Serious

Six of them were prospective studies [7, 8, 9, 13, 14, 15] and seven were retrospective cohort studies [10, 11, 12, 16, 17, 18, 20]. An initial bolus dose of 5 mg was administered in 7 studies [7, 9, 11, 12, 13, 15, 17] while in one study the starting dose was 7.5 mg [8]. In order to improve the visualization of the structures that is often distorted from ICG overdose some surgeons adapted their dosing protocols lowering their initial dose. Angell et al. [10] reported using a test dose of 1.25 mg followed by an additional same dose, provided that differential fluorescence is achieved, right before clamping. They claim to have highly reliable results regarding tumor identification. Similarly, Sentell et al. [18], suggested a dosing scheme with a starting dose of 0.625 mg ICG when using Da Vinci Xi robot and 1.25 mg when using Da Vinci Si, followed by a re-dose of 0.825 mg and 1.875 mg respectively. They successfully achieved differential fluorescence in a large majority of tumors during robotic assisted PN with an exceedingly low positive margin rate (0.3%) which they attribute to their dosing scheme.

The reported time interval between injection and fluorescence of the vasculature or the renal parenchyma ranges from five seconds to two minutes [7, 11, 13, 15–20] with one minute considered adequate time in most of the studies. An extra ICG dose after tumor excision and the performance of the renorrhaphy was given by some authors in order to confirm that kidney is fully perfused [7, 8, 14, 15, 16]. The dosage schemes used in each study are summarized in Table 3.

Table 3. *The dosage schemes used in each study*

Study	Individual dose	Number of doses/ Patient
Tobis et al. (2011) [7]	5 mg	3
Borofsky et al. (2012) [8]	7.5 mg	2
Krane et al. (2012) [9]	5 mg	1
Angell et al. (2013) [10]	1.25 mg	2
Harke et al. (2013) [11]	5 mg	1
Bjurlin et al. (2014) [12]	5 mg	1
Lanchon et al. (2018) [13]	5 mg	1
Simone et al. (2018) [14]	1.5 ml ICG + 0.75 ml lipiodol	2
Mattevi et al. (2018) [15]	5 mg	2
Diana et al. (2020) [16]	5–10 mg	2
Gadus et al. (2020) [17]	5 mg	1
Sentell et al. (2020) [18]	0.625–1.25 mg	2
Wang et al. (2021) [19]	2.5 mg	1
Yang et al. (2022) [20]	7.5–12.5 mg	1

Ischemia time

In our review global ischemia time, defined as the clamping of the main renal artery was applied in four studies [7, 10, 19, 20], selective ischemia time was applied in six studies [8, 11–15,] and a mixed approach in 3 studies [9, 10, 11]. The mean warm ischemia time (WIT) on each study ranges from 11.6 minutes to 27.2 minutes [7–18, 20]. Someone

Table 4. *Estimated blood loss and positive surgical margins rates*

Study	Estimated blood loss (ml), mean	Positive surgical margins, n (%)
Tobis et al. (2011) [7]	181	0 (0)
Borofsky et al. (2012) [8]	206.5	0 (0)
Krane et al. (2012) [9]	165	3 (6.4%)
Angell et al. (2013) [10]	103	0 (0)
Harke et al. (2013) [11]	347	0 (0)
Bjurlin et al. (2014) [12]	200	2 (3.8%)
Lanchon et al. (2018) [13]	131	1 (3.3%)
Simone et al. (2018) [14]	266.6	0 (0)
Mattevi et al. (2018) [15]	206	0 (0)
Diana et al. (2020) [16]	123.3	11 (3.5%)
Gadus et al. (2020) [17]	190	3 (8%)
Sentell et al. (2020) [18]	112.2	1 (0.3%)
Wang et al. (2021) [19]	48.2	0 (0)
Yang et al. (2022) [20]	93.3	2 (11%)

would expect a lower ischemia time to the studies were the main renal artery was clamped due to the bloodless field, however, that was not proved from the available studies probably because it is affected by other factors that were not examined, such as the surgeon's competence and the tumor characteristics. While there is lack of prospective comparative studies in the current literature comparing PN with and without the use of ICG, three studies included in our review conducted a retrospective and/or matched-pair analysis for patients undergoing PN with and without ICG [9, 19, 20]. Superiority of PN with NIRF over traditional PN without ICG, in terms of warm ischemia time was observed by Krane et al. The mean WIT in the group of ICG was 16.3 minutes compared to 19.66 minutes in the control group ($p < 0{,}001$). In a more recent study, Yang et al. presented reduced WIT by four minutes when NIRF with ICG was implemented (mean WIT 21.33 minutes vs 25.33 minutes) [20].

Estimated GFR reduction

Eleven studies were included in the analysis of eGFR reduction after PN with the use if ICG [8, 9, 11–17, 19, 20]. Assessment of renal function was available for all patients at discharge at seven studies [9, 11, 13, 14, 16–19]. The reported eGFR reduction ranged from 0% [13] to 15.47% [19] in these studies. In three studies eGFR reduction was calculated at 1 month post op with mean rates of 0.3% [15] 1% [13] and 1.8% [8]. At six months follow up, eGFR reduction was 2% [13] and 15.77% [20] in two studies.

NIRF using ICG dye has been incorporated in robotic PN not only as an auxiliary mean for tumor identification but also as a helpful tool in performing selective ischemia and by extension renal functional preservation. In our review this seems to be achieved, as studies where selective ischemia was performed had lower eGFR reduction rates compared to studies with global ischemia (e.g., 6.2% [11] vs 15.47% [19]). However, these results should be interpreted with caution as they need to be further determined by prospective randomized studies of larger scale.

Estimated blood loss and positive surgical margins

In terms of blood loss, PN with the use of NIRF with ICG dye presented EBL rates that are in line with published literature for PN [24, 25]. Lowest mean EBL rate was 48.2 ml [19] and the highest was 347 ml [11]. Furthermore, there were no clinically significant differences in EBL between studies where NIRF was used to facilitate selective ischemia [8, 11–15,] and studies where NIRF was used for tumor identification with main renal artery clamping [7, 10, 19, 20] (see Table 2).

Regarding positive surgical margin rates, 7 studies did not present positive surgical margins [7, 8, 10, 11, 14, 15, 19] while in the rest of the studies involved in our analysis PSM rates were 6.4% [9], 3.8% [12], 3.3% [13], 3.5% [16], 8% [17], 0.3% [18] and 11% [20]. EBL and PSM rates are summarized in Table 4.

DISCUSSION

Surgical treatment of renal cancer has faced many changes over the last twenty years due to the ongoing development of robotic surgery and imaging technology. While partial nephrectomy was first indicated for small renal masses has now been extended to cases with larger masses whenever feasible [26]. There is also an ongoing trend towards kidney preservation shifting the concept of trifecta during PN to pentafecta to encompass renal functional preservation [27]. The use of ICG that has been adopted to enhance these efforts for kidney preservation, has demonstrated a high safety and convenience profile in our review. The dosing schemes are more or less the same, however a standardized ICG dose has to be defined. Most import advantage of utilizing ICG in PN seems to be the selective ischemia that can be achieved. Selective clamping with NIRF using ICG seems to be technical feasible and safe without compromising surgical margins, as it guarantees a nearly blood-less tumor resection. Thus, eGRF is not dramatically reduced, demonstrating lower

reduction rates when compared with global ischemia (e.g., 6.2% [11] vs 15.47% [19]). Moreover, the 25 minutes that Hung et al. [28] suggested as the maximum WIT for optimal postoperative performance in terms of renal function were not surpassed in most cases were global ischemia with ICG was performed [7, 10, 20]. In a recent study from Yang et al., WIT was reduced by four minutes when NIRF with ICG was implemented compared to the group without ICG use (mean WIT 21.33 minutes vs 25.33 minutes) [20]. Similar results were presented by Krane et al. The mean WIT in the group of ICG was 16.3 minutes compared to 19.66 minutes in the control group ($p < 0{,}001$). Regarding positive surgical margin rates, they were consistently low (0% to 11%) and in line with published literature (PSM between 0–10%), confirming the efficacy of the technique [29–32].

Despite the aforementioned positive results PN using ICG has its limitations primarily being more suited for tumors that are superficially localized, as its tissue penetration is limited. However, research has been conducted to increase its penetration depth and make it suitable for endophytic renal masses. One study mixed ICG with lipiodol to prevent quick washout from the renal tumor [11]. The lipiodol-ICG mixture was superselectively transarterially delivered before surgery, and a postprocedural CT scan was done for localization. The outcome of this method on completely endophytic tumors was positive, with no intraoperative and postoperative complications observed, and acceptable renal functional outcomes.

Tumor complexity is a very important factor in PNs, especially in terms of tumor identification and anatomical dissection. In our review the included studies demonstrated tumors with a range in median RENAL score from 6 to 9 rated as of low and moderate complexity respectively. We have to say that no considerable discrepancies were observed between these studies regarding oncological or functional outcomes. However, we have to admit that we cannot draw safe conclusions due to the small sample size of most of the studies and the lack of randomized controlled trials. Future prospective randomized studies are indubitably essential in order to assess whether the utilization of NIRF technology can improve results in more complex tumors comprising RENAL scores of 10 and above.

Limitations of our present study include the absence of randomized controlled trials, the retrospective nature of many of the studies included, the relatively small sample sizes and the lack of long follow-up time in most of them. However, to the best of our knowledge this is the first attempt to present a thorough review of a technique which was first received with enthusiasm by urologists but has relatively been abandoned, considering the lack of attention in the current literature.

CONCLUSIONS

Indocyanine green seems to be a useful tool in partial nephrectomy as it can assist surgeons in identifying tumor and its related vasculature. Thereby, warm ischemia time can be reduced and, in some cases, selective ischemia can be implemented leading to better renal functional preservation.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

UROLOGICAL ONCOLOGY

The presence of cribriform pattern in prostate biopsy and radical prostatectomy is associated with negative postoperative pathological features

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Introduction Prostate cancer is the second most common male cancer worldwide. Its rising incidence and high overtreatment rate drive the search for new prognostic factors. Histopathological variants, such as cribriform pattern (CP), are associated with poorer oncologic outcome. The aim of this study was to assess the correlation between CP in prostate biopsy and radical prostatectomy (RP) and postoperative pathological features.

Material and methods In this retrospective, single-centre study we analysed the reviewed medical records of 100 men who underwent minimally invasive RP in the years 2017–2019. RP histopathological examination was performed by a single expert pathologist, and preoperative biopsies were assessed by various professionals from different referral centres.

Results 48% of men underwent endoscopic RP with limited lymphadenectomy, whereas 52% underwent laparoscopic RP with extended lymphadenectomy. CP in biopsy was present in 6 patients: 3 in each of both groups (6.3% and 5.8%, respectively). Lymph node metastases were present in 50% and 10% of patients with and without CP in biopsy, respectively ($p = 0.028$). Postoperative histopathological examination revealed CP in 65%. CP in RP was associated with higher International Society of Urological Pathology (ISUP) ($p < 0.001$), extraprostatic extension (EPE) ($p = 0.001$), seminal vesicle invasion (SVI) ($p = 0.001$), and positive surgical margin (PSM) ($p = 0.004$). Thirteen (20%) of the patients with CP in the RP specimen had lymph node metastasis, and none of the patients without CP in the RP specimen had regional LN metastasis.

Conclusions The presence of CP in a biopsy specimen and RP is associated with negative postoperative features. Therefore, efforts should be made to increase CP reporting in biopsies because its identification could trigger a more radical surgical approach with extended lymphadenectomy.

Key Words: cribriform pattern ‹› prostate cancer ‹› radical prostatectomy ‹› prostate biopsy

INTRODUCTION

Prostate cancer (PCa) is the second most common male cancer worldwide. The high incidence and clinical impact of radical treatments on patients' quality of life stimulate clinicians to further improve diagnostic methods and seek parameters that could help better discriminate clinically significant (CSPCa) from non-significant prostate cancer (NSPCa). Currently, the shared decision-making process is still based on D'Amico risk group classification, which incorporates the following vari-

ables: serum prostate specific antigen (sPSA), clinical disease stage, and morphology of cancer cells in prostate biopsy. Nonetheless, those parameters are not ideal and carry the risk of both over- and underestimation of the disease. The 2014 International Society of Urological Pathology (ISUP) consensus conference on novel assessment of prostate biopsy and radical prostatectomy (RP) specimens acknowledged that cribriform pattern (CP) along with ill-formed glands, fused gland, and glomeruloid structures were to be recognized as a spectrum of Gleason 4 pattern. The reported prevalence of cribriform morphology varies significantly between studies from 8.9% [1] to 37% (cribriform architecture, not solely CP) [2] in prostate biopsy and from 25% [3, 4] to almost 70% in radical prostatectomy specimens [2, 5]. Until recently there was no uniform definition of CP. In 2021 the ISUP held a conference, and recognized experts in the field of uropathology developed a consensus definition of CP. Currently, CP is defined as a confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power [6]. There should be no intervening stroma or mucin separating individual or fused glandular structures [7]. To date, conducted studies have shown an association between CP in both prostate biopsy and RP specimens, and adverse pathological findings and clinical outcomes after RP such as more advanced disease stage, lymph node metastasis (LNs met), shorter biochemical recurrence (BCR)-free survival, higher risk of distant metastasis, and shorter disease-specific survival (DSS) [5, 8, 9, 10]. The negative impact of regional LN metastasis especially in multiple LNs on oncological outcomes in PCa patients has also been proven [11, 12]. The extent of lymphadenectomy (LND) during RP depends on the risk of lymph node involvement based on available nomograms. Limited LND (lLND) is restricted to obturator LNs, whereas extended pelvic lymphadenectomy (ePLND) additionally involves the removal of LNs overlying external and internal iliac vessels. Histopathological evaluation of removed lymphatic tissue provides valuable information on the disease stage and helps guide adjuvant treatment. At the same time, studies conducted to date have failed to confirm that LND is associated with any oncological benefit. ePLND provides more tissue for analysis but is associated with higher morbidity, especially lymphocele [13, 14]. The authors decided to conduct this study to evaluate the impact of CP at biopsy and RP on pathological adverse findings after RP and to assess real-life reporting of CP in prostate biopsy specimens.

MATERIAL AND METHODS

In this retrospective, single-centre study we analysed the reviewed medical records of 100 patients treated with minimally invasive RP for localised or locally advanced PCa from 2017 to 2019. Patients who were either primarily managed with external beam radiotherapy (EBRT) or received neoadjuvant androgen deprivation therapy (ADT) or in whom data from medical history regarding prostate biopsy or RP were incomplete were excluded from further analysis. Minimally invasive RP was performed by a single high-volume expert surgeon. The decision regarding the need for ePLND was based on the 2012 Briganti nomogram available online. When the risk of lymph node metastases < 5%, ePLND was omitted and lLND was performed. The histopathological examination was performed by a single expert pathologist following the 2014 ISUP criteria. Preoperative biopsy results were extracted from patients' medical records. Details regarding the prostate biopsy technique were not taken into consideration because in most cases those data were missing. Patients' clinical characteristics included the following: age at the time of surgery, preoperative sPSA, PSA density (PSAD), clinical disease stage according to the 2017 UICC TNM classification system, and multiparametric resonance imaging results (mpMRI). Extracted biopsy characteristics were as follows: ISUP according to 2014 ISUP recommendations, percentage of cores involved by the PCa, the presence of CP and intraductal carcinoma (IDC). Pathological assessment of RP specimen included the following: type of surgery, the extent of LND, pathological disease stage according to the 2017 UICC TNM classification system, ISUP according to 2014 ISUP recommendations, PCa extension (one vs. both lobes), extraprostatic extension (EPE), seminal vesicle invasion (SVI), positive surgical margin (PSM), lymph node metastases (LNs met), and the presence of CP and IDC. The examining expert uropathologist used the CP definition provided by the 2014 ISUP recommendations [15]. No attempt was made to identify large and small CPs. IDC was identified with the WHO 2016 definition. Basal cell immunostaining to distinguish between CP and IDC was left to the discretion of the examining expert uropathologist. The primary endpoint of this study was to assess the impact of CP in prostate biopsy and RP on disease stage and adverse pathological parameters in RP specimens. The secondary endpoint was concordance between biopsy and RP in the detection of CP.

Statistical analysis

Data on categorical variables were reported as frequencies (n) and percentages (%). Continuous variables were described as means ± standard deviations (SD) or median values and interquartile range (IQR). To assess continuous variables between CP and non-CP, a t-test was used if the normal distribution was confirmed; otherwise, the Mann-Whitney U test was used. The chi-square and Fisher exact tests were used to compare categorical variables between CP and non-CP. Prostatectomy findings on CP were considered as a gold standard to determine sensitivity and specificity of prostate biopsy. A P-value of <0.05 was considered significant. All statistical analyses were performed with jamovi (Version 2.3).

RESULTS

Baseline cohort characteristics

The entire cohort consisted of 100 patients. The mean age at the time of the surgery was 63.9 years (SD ±6.6). The mean sPSA level was 11.9 ng/ml (SD ±10.2). In 47 patients mpMRI was performed with a mean prostate volume of 44.9 cc (SD ±26). Thirty-nine of those men underwent mpMRI in the pre-biopsy setting. In 32 patients, data regarding the number of biopsy cores were missing, and in the remaining 68 cases the mean number of cores per patient was 7.9. In total, 48 men underwent extraperitoneal endoscopic radical prostatectomy (EERP) with lLND, whereas in 52 patients laparoscopic radical prostatectomy (LRP) with ePLND was performed. After RP, upgrading was observed in 47% and downgrading in 21% of patients, respectively.

Clinicopathological features in patients with and without cribriform pattern in prostate biopsy

Among 100 men, biopsy revealed CP in 6 cases. Neither PSA nor PSAD differed significantly between patients with and without CP in prostate biopsy. One-third of patients with (n = 2) and 13% without (n = 12) CP in prostate biopsy, respectively, had clinically locally advanced disease. Fifty per cent of patients with CP in prostate biopsy underwent either EERP with lLND or LRP with ePLND. CP was significantly associated with lymph node metastasis (LNs met) (p = 0.028) and the presence of IDC in the RP specimen. There was no statistically significant correlation between CP and other negative pathological features. (Table 1)

Clinicopathological features in patients with and without cribriform pattern in radical prostatectomy specimen

Patients with CP in the RP specimen were more likely to have clinically more advanced disease ($p< 0.001$). Moreover, CP in RP was associated with higher ISUP ($p < 0.001$). Pathological negative prognostic factors such as EPE (p = 0.001, RR 1.68 [1.26–2.25]), SVI (p = 0.001, RR 1.47 [1.22–1.76]), PSM (p = 0.004, RR 1.32 [1.13–1.54]) were also more commonly encountered in CP-positive patients. Thirteen (20%) patients with CP in the RP specimen had regional LNs met.

Table 1. *Clinicopathological characteristics of patients with and without cribriform pattern in prostate biopsy*

RP	CP in Bx	non-CP in Bx	p-value
Number, n (%)	6 (6)	94 (94)	
Age (mean ± SD)	64.8 ±8.57	63.8 ±6.54	0.721[&]
MRI PV (cc) (mean ±SD)	40.4 ±28.2	45.5 ±26.0	0.309[*]
PSA (ng/mL) (mean ±SD)	12.1 ±11.1	11.8 ±10.2	0.667[*]
cTNM, n (%)			
cT1	2 (33)	46 (49)	
cT2a/b	2 (33)	26 (27)	
cT2c	0	10 (10)	
cT3	2 (33)	12 (13)	0.369[*], 0.308[&]
Surgery, n (%)			
EERP + lLND,	3 (50)	45 (48)	
LRP + ePLND	3 (50)	39 (41)	1.000[#]
Lobe, n (%)			
One	2 (33)	46 (49)	
Both	4 (67)	41 (44)	0.425[#]
ISUP, n (%)			
1	0 (0)	4 (4)	
2	1 (17)	41 (44)	
3	2 (33)	37 (39)	
4	2 (33)	6 (6)	
5	1 (17)	6 (6)	0.053[#]
Upgrading, n (%)	1 (17)	46 (49)	0.210[#]
ECE, n (%)	4 (67)	35 (37)	0.205[#]
SVI, n (%)	3 (50)	20 (21)	0.133[#]
PSM, n (%)	1 (17)	17 (18)	1.000[#]
N1, n (%)	3 (50)	10 (10)	0.028[#]
IDC, n (%)	3 (50)	9 (10)	0.022[#]

Bx – prostate biopsy, RP – radical prostatectomy, CP – cribriform pattern, MRI – magnetic resonance imaging , PV – prostate volume, ISUP – International Society of Urological Pathology classification, PSAD – PSA density, EERP – endoscopic extraperitoneal radical prostatectomy, LPR – laparoscopic radical prostatectomy, lLND – limited lymphadenectomy, ePLN – extended pelvic lymphadenectomy, ECE – extraprostatic extension, SVI – seminal vesicle invasion, PSM – positive surgical margin, N1 – regional lymph node metastasis: obturator, external iliac, internal iliac, IDC – intraductal carcinoma
[&]t-test; [*]Mann-Whitney U-test; [#]Fisher's exact test

Cribriform pattern and intraductal carcinoma in prostate biopsy and radical prostatectomy specimens

The prevalence of CP in RP specimens was 65%, which was much higher than in biopsies (6%). In patients with CP in the prostate biopsy, RP confirmed the diagnosis in 5 cases. Additionally, CP was detected in another 60 patients without CP in the biopsy.

Table 2. *Clinicopathological characteristics of patients with and without cribriform pattern in radical prostatectomy*

RP	CP in RP	non-CP in RP	p-value	RR (95% CI)
Number, n (%)	65 (65)	35 (35)		
Age (mean ±SD)	64.1 ±6.3	63.5 ±7.29	0.634[&]	
MRI PV (cc) (mean ± SD)	41 ±19.4	51.3 ±33.7	0.319*	
PSA (mean ±SD)	14.2 ±11.9	7.52 ±3,06	0.012*	
PSAD (mean ±SD)	0.322 ±0.327	0.176 ±0.096	0.176*	
cTNM, n (%)				
cT1	23 (35)	25 (71)		
cT2a/b	20 (31)	8 (23)		
cT2c	9 (14)	1 (3)		
cT3	13 (20)	1 (3)	< 0.001*	
Surgery, n (%)				
EERP+lLND	26 (40)	22 (63)		
LRP+ePLND	39 (60)	13 (37)	0.37[@]	2.54 (1.09–5.92)
Lobe, n (%)				
One	26 (40%)	22 (63%)		
Both	34 (52%)	11 (31%)	0.032[@]	1.54 (1.06–2.24)
ISUP, n (%)				
1	0 (0)	4 (11)		
2	19 (29)	19 (54)		
3	33 (51)	10 (35)		
4	6 (9)	2 (6)		
5	7 (11)	0 (0)	< 0.001*	
ECE, n (%)	33 (51)	6 (17)	0.001[@]	1.68 (1.26–2.25)
SVI, n (%)	22 (34)	1 (3)	0.001[@]	1.47 (1.22–1.76)
PSM, n (%)	17 (26)	1 (3)	0.004[@]	1.32 (1.13–1.54)
N1, n (%)	13 (20)	0		
IDC, n (%)	9 (14)	3 (9)	0.533[@]	1.71 (0.43–6.79)

RP – radical prostatectomy, CP – cribriform pattern, RR – relative risk, CI – confidence interval, MRI – magnetic resonance imaging, PV – prostate volume, ISUP – International Society of Urological Pathology classification, PSAD – PSA density, EERP – endoscopic extraperitoneal radical prostatectomy, LPR – laparoscopic radical prostatectomy, ILND – limited lymphadenectomy, ePLND – extended pelvic lymphadenectomy, ECE – extraprostatic extension, SVI – seminal vesicle invasion, PSM – positive surgical margin, N1 – regional lymph node metastasis: obturator, external iliac, internal iliac, IDC – intraductal carcinoma
[&]t-test; *Mann-Whitney U-test; [@]chi-square test

In one case cribriform structures were only found on core biopsy material, not in the material from RP. Sensitivity and specificity of CP detection in prostate biopsy were 7.7% and 97%, respectively. RP specimen evaluation identified IDC in 50% and 10% of patients with and without CP in prostate biopsy ($p = 0.02$), respectively. Altogether there were 68 patients with CP/IDC in RP specimens.

DISCUSSION

We performed this study to evaluate the impact of CP in prostate biopsy and RP on adverse pathological findings after RP and to assess real-life reporting of CP in biopsy in a retrospective cohort. The results show that the presence of CP in prostate biopsy as well as RP is a negative pathological prognostic factor and that in our setting CP detection in biopsy specimens seems to be underreported. Additionally, patients positive for CP in biopsy had significantly more frequently concurrent IDC in RP.

In our study, CP was identified in 6% and 65% in prostate biopsy and matched RP specimens, respectively. The 2014 ISUP conference consensus concluded that Gleason 4 pattern spectrum includes 4 different submorphologies: CP, ill-formed glands, fused glands, and glomeruloid structures [15]. Although combined in one group, these patterns seem to have different malignant potential, which was not included in recent guidelines [5, 9]. Until recently there was no uniform CP definition. With the new consensus CP definition there are still inconsistencies amongst pathologies regarding the minimal size of lesions containing cribriform structures. Moreover, sole microscopic examination can be challenging in distinguishing between CP and IDC. Therefore, immunohistochemical staining for basal cells is recommended in equivocal cases. Multiple studies showed conflicting results regarding the true prevalence of CP in both RP and prostate biopsy. Elfandy et al. assessed the prevalence of CP in RP specimens based on the analysis of The Cancer Genome Atlas cohort (TCGA) and identified CP in 62% of cases, but they made no attempt to distinguish CP from IDC [16]. Boettcher et al. assessed combined CR/IDC presence in the same cohort, and despite inclusion of IDC, fewer CP/IDC cases were detected (31%) [17]. According to Masoomian et al., the prevalence of CP/IDC in prostate biopsy and RP was 26.9 % and 51.8%, respectively. Keefe et al. proved good interobserver agreement ($K = 0.79$) in CP identification in prostate biopsy specimens [18]. Satisfactory interobserver reproducibility in terms of CP detection in contrast to the other GP 4 patterns such as ill-formed or fused glands was also

reported by Kweldam et al. [19]. Hollemans et al. found cribriform architecture in 30% (55/186) of prostate biopsies and 69% (128/186) of matched RPs, with a sensitivity of 43% and specificity of 97%; it is worth mentioning that in the study both biopsy and RP specimens were reviewed by 3 investigators [2]. Downes et al. showed comparable results in terms of sensitivity and specificity (30% and 97%) in CP identification in prostate biopsy [20]. To further improve pathological identification of CP, in 2021 the ISUP held a conference, and recognized experts in the field of uropathology developed a consensus definition of CP [6]. In our study, the high specificity (97%) was in line with aforementioned results. However, the very low sensitivity (7.7%) was unexpected. We assume that a major factor contributing to this surprisingly low sensitivity is the origin of the biopsy data. In our cohort prostate biopsy was performed in different centres across the country. The information regarding prostate biopsy was derived from patients' medical records, and therefore it raised questions about the quality of tissue sampling, pathological evaluation, and reporting. The problem of CP presence reporting in prostate biopsy was reflected by the results of a pre-meeting survey for the Genitourinary Pathology Society (GUPS), which took place in 2019 and revealed that only 40% of US pathologists confirmed inclusion of CP in biopsy PCa diagnosis. A study by Hollemans et al. showed that biopsy undersampling may lead to false negative results in up to 40% of cases [2].

CP is considered as a highly aggressive PCa morphology. The presence of CP in RP has been shown to be associated with both adverse pathological and oncological outcomes such as the following: advanced disease stage, PSM, shorter BCR-free survival, shorter MFS-free survival, and shorter OS [9, 10, 21]. CP in prostate biopsy has also been found to be a negative prognosticator after RP: postoperative disease upgrading, upstaging, and LN metastasis [18, 22]. We found no association between CP in prostate biopsy and EPE, SVI, PSM, and disease upgrading after RP, probably as a result of low CP prevalence. Fifty per cent of patients with CP in prostate biopsy underwent either lLND or ePLND. LN metastases were identified in 50% (n = 3) and 10% (n = 10) of patients with and without CP in prostate biopsy, respectively (p = 0.03). The extent of LND is determined by the risk of harbouring LN metastasis. Widely available externally validated nomograms such as the Briganti nomogram, the Roach formula, or the Partin and MSKCC nomograms help clinicians in preoperative assessment of LN invasion [23]. Those nomograms include various variables such as sPSA, clinical disease stage, biopsy ISUP, and the number of positive cores. A recently developed risk calculator by Briganti includes mpMRI findings to better discriminate the high-risk population. However, none of those nomograms incorporates prostate cancer cell morphology. Moreover, EAU guidelines do not consider inclusion of CP in the decision-making process regarding the extent of LND. In the case of elevated probability of LN metastasis, ePLND is recommended. Although this study showed that LN metastases were statistically more common in patients with CP in prostate biopsy, only half of them underwent LRP with ePLND. LNs met, especially in multiple LNs, are a known negative prognostic factor associated with worse BCR-free survival, MET-free survival, and OS [24–25]. Whether LND during RP influences oncological outcomes remains controversial; however, it provides detailed information on the disease stage and may guide adjuvant treatment [26].

CP is characterized by distinct genetic and epigenetic alternations, which are indicative of its highly aggressive behaviour. Based on the analysis of the TGCA cohort, cribriform morphology was characterized by deletions of multiple genes: PTEN (10q23.3), NKX3–1 (8p21.2), and MAP3K7 (6q15), which, as tumour suppressor genes, play crucial roles in malignant transformation. PTEN and NKX3–1 loss is more commonly encountered in metastatic castration resistant PCa (mCRPC) [27]. Moreover, expression alternations also affect other tumour suppressor genes such as RB1 and TP53, which are also known to be associated with more aggressive PCa behaviour and therapy resistance [28, 29]. The methylation level is higher in patients with cribriform morphology compared to non-cribriform. Significant hypermethylation affect multiple genes such as CYP26A, ZNF853, DDIT4L, B3GAT1 and RASL12. Methylation profile alternations have also been found in other genes such as EVX1, EPHX3 (ABHD9) and IRAK3 [27]. All these epigenetic changes show that cribriform morphology methylation profile resembles mCRPC. Genetic changes in CP also affect RNA expression. Long noncoding RNA SChLAP1 has been found to be increased in case of CP [30]. At the same time overexpression of SChLAP1 has been linked to increased metastatic burden [31]. There are multiple genetic pathways in which CP acquires its malignant behaviour.

MpMRI plays a crucial role in the process of PCa diagnosis and further management. There are inconclusive results on the issue of CP visibility on mpMRI. Seyrek et al. and Tuna et al. reported that CP-containing lesions are visible in mpMRI [32, 33]. The lesions were also characterized by low ADC values. Mikoshy et al., on the other hand, concluded

that mpMRI detectability is more depended on relative fractions of cells, stroma, and luminal space rather than typical architectural pattern [34].

In our study IDC in RP specimens was detected in 50% and 10% of patients with and without CP in prostate biopsy, respectively (p = 0.022). According to the 2014 ISUP consensus, IDC is a separate histopathological pattern that is not included in the grade group system [15]. In 2016 the WHO released a novel pathological classification of prostate tumours and provided a unified definition of IDC, a newly recognized entity, which is defined as an intra-acinar and/or intraductal neoplastic epithelial proliferation, which has some features of high-grade prostatic intraepithelial neoplasia (HGPIN) but exhibits much greater architectural and/or cytological atypia [35]. IDC in prostate biopsy and RP has been shown to be associated with adverse outcomes, more advanced disease stage, LN metastasis, shorter BCR-free survival, and worse cancer-specific survival (CSS) [36, 37, 38]. Masoomian et al. confirmed the negative impact of the presence of CP/IDC at biopsy on more advanced disease stage (p = 0.013). The authors also highlighted in meticulous and careful evaluation of specimens that CP/IDC presence in prostate biopsy in both true positive and false negative cases was linked with more advanced PCa stage [39]. Kweldam et al. showed that CP/IDC in prostate biopsy was associated with worse disease-specific survival (DSS). ISUP 2 patients without CP/IDC had DSS comparable to men with ISUP 1 PCa. On the other hand, ISUP 2 patients with CP/IDC had significantly worse survival than ISUP 2 patients without CP/IDC, and hence they should be discouraged from AS [23].

The malignant potential of CP is reflected in the current EAU guidelines, which recommend mandatory reporting of the presence of CP/IDC in prostate biopsy. Additionally, both CP and IDC are considered as an absolute contraindication for active surveillance (AS) [26]. The American Urological Association (AUA) also discourages AS in CP/IDC-positive patients [40]. The question regarding the best radical treatment option in patients with CP remains to be answered.

Our study has caveats that need to be addressed. Firstly, it was a retrospective and single-centre study with a small cohort. A lack of data led to the disqualification of a considerable number of patients treated for PCa in the given timespan. Secondly, the absence of biopsy re-evaluation and data collection from patients' medical records impacted the study bias. In our setting – a tertiary referral department of urology – we manage patients who underwent prostate biopsy outside our department, which in turn makes biopsy slides practically inaccessible. This study, however, presents a real-life scenario, in which the true prevalence of CP in prostate biopsies seems to be underreported. Moreover, identification of CP in RP specimens was based on a single expert opinion. At least 2 expert genitourinary pathologists would be optimal. In light of this study, we assume that uropathologists should place more emphasis on detailed and careful evaluation of both prostate biopsies and RP specimens because the cancer cell morphology has an impact on the patients' prognosis.

CONCLUSIONS

CP is a negative pathological feature after RP. Although cancer cell morphology is not currently incorporated in any tools predicting LN involvement, it may provide additional information on the disease stage and guide the extent of LNs during radical treatment. Additionally, pathological evaluation of both prostate biopsies and RP specimens requires special expertise and vigilance from uropathologist in the detection of CP because its presence matters and may have an impact on decisions regarding the patients' treatment and prognosis.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

UROLOGICAL ONCOLOGY

Initial experience of the Versius robotic system in robot-assisted radical prostatectomy: a study of 58 cases

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Introduction The study presents the initial outcomes of robot-assisted radical prostatectomies (RARPs) using the Versius robotic system in a urological centre with no prior robotic surgery experience.
Material and methods A retrospective analysis of 58 RARPs was conducted, including patients' parameters as well as Versius system performance.
Results The study involved 58 patients (average age 66.9 years). Median preoperative prostate specific antigen (PSA) was 9.8 ng/ml, with 48% having ISUP grade group ≥ 3 on biopsy and 25.8% showing extraprostatic extension on MRI. Median blood loss was 437 ml, with complications (10.3% Clavien-Dindo grade II and 4 grade III cases). One conversion to open surgery occurred (0.58%). Final pathology revealed 46.5% extraprostatic disease, and 25.8% had positive margins. Post-surgery, 96.5% had undetectable PSA at 6 weeks. Continence rates were 89.7% at 6 weeks, increasing to 91.3% at 12 months. Median catheter duration was 7.9 days, and the hospital stay was 4.5 days. Console time averaged 150.9 minutes, with a median operative time of 213 minutes. The Versius system reported medium priority alarms in 24.1% of operations, including 1266 alarms related to robotic arm clashes and 43 instrument swaps. One bedside unit exchange occurred with no console or robotic system failures.
Conclusions The Versius robotic system can be successfully introduced in a urological centre without prior robotic surgery experience. Our setup and operating room positioning are effective, safe, and reproducible. We encountered and resolved surgical and technical challenges. Further follow-up studies are needed to assess the system's performance.

Key Words: prostatectomy ‹› robotic system ‹› robot-assisted radical prostatectomy ‹› Versius

INTRODUCTION

Since the beginning of the twentieth century, robotic technology has brought changes to various surgical specialties, including urology. Even though a definition of a word 'robot', first used by Czech novelist Karel Čapek in 1921, refers to an autonomous machine resembling a human being and replicating its movements and tasks, it does not precisely apply to current surgical robots. Nevertheless, it has sparked an exciting vision for the future of surgery, which is expected to evolve further [1].
Admittedly, not all available data have demonstrated the clear clinical benefits of these new systems. However, both patients and surgeons are increasingly seeing robotic surgery as the next step in the evolution of surgical techniques. Up to now, the key improvement has been a manipulation capability with wrist-like instrument movements, but there are more to come, with haptic sensation, remote operations, and telemetric measurements among others [2, 3].
Recently, the robotic market has undergone significant changes with various companies entering the market, leading to costs reductions and increased accessibility to this technology [4, 5]. Some companies, like Intuitive, have continued to develop established principles and create machines like Da Vinci, while others have explored alternative solutions. One such

system is the Versius robot, developed by CMR Surgical in Cambridge, UK, and introduced to the market in 2020.

The Versius system comprises an open surgeon's console with a pistol-like controller handgrip and a visualization bedside unit (BSU) equipped with a 3D vision camera and 2–3 independent operative BSUs for wristed instruments. The instruments offer 7 degrees of freedom at the tip and provide 720 degrees of rotation. The handgrip controller manages the camera, and a clutch integrated into the handgrip operates without the need for foot controls. The system also offers constant telemetric and visual recording of the procedure.

CMR has successfully miniaturized the robotic system, making it suitable for use in most surgical rooms without the need for special preparation. The instruments are 5 mm in diameter, and the Versius system is both portable and transportable. Its modular design allows individual arms to be moved within the operating room or to different operating rooms in the hospital without requiring any alterations.

The usage of the Versius system for RARP has been explored in preclinical studies on cadavers [6, 7] and live patients [8]. This study aims to present the short-term clinical results of the first 58 RARPs performed with the assistance of the Versius robot for prostate cancer patients in a medical centre with no prior experience in robotic surgery.

MATERIAL AND METHODS

A retrospective analysis was conducted on 58 consecutive patients who underwent RARP between July 2022 and December 2022. The first 5 surgeries were performed under the supervision of a proctor (S.G.), who had prior experience using the Versius robotic system with the same surgical prostatectomy technique and operating theatre setup.

All members of the surgical team participated in official technical training, which included theoretical and practical sessions, including cadaver operations, provided by the company in laboratory settings.

Prior to surgery, all patients were informed about the setup and details of the Versius robotic platform, as well as the use of collected data for analysis. Informed consent was obtained from all patients.

During the procedures, all patients were positioned in a 20-degree Trendelenburg position, with their legs slightly lowered to increase the angle between the upper body and pelvis, facilitating better access to the prostate under the pubic bone and reducing the risk of collision between the robotic arms and the pubic bone. A 12 mm endoscope port was placed 2–3 cm above the umbilicus along the midline. Two dedicated 7 mm 'Yellowports' for the robotic arms, specific to this robotic platform, were placed under direct visualization on a transversal line on both sides, approximately 5–6 cm below the optic port. The placement of the robotic ports varied between 9 and 12 cm apart, depending on the patient's anatomy and BMI. Measurements were taken after inflation of the abdomen with CO_2. Additionally, one 5 mm trocar for a suction-irrigation device and one 12 mm trocar for the laparoscopic clipper were placed on the right side of the abdomen to assist the surgeon, as shown in Figure 1.

The Versius robotic system consists of independent robotic units with cart-mounted arms, which require a dedicated setup before the operation. Part of this set up is the port training, which secures 'system self-orientation' of trocars performed by the surgical team in a step-by-step procedure to calibrate the instrument pivot points and align them with the targeted zone. This calibration is crucial for ensuring precision during the surgery.

The adaptation of the port configuration is carried out based on the patient's features, the position of the robotic units, and the instrument length. The unit cart's footprint is 38 × 38 cm, allowing for comfortable placement around the operating table to provide good access to the patient throughout the entire operation. The angles of the robotic arms and the height of the units were assessed by the surgical team, optimizing the working space for the table assistant on the right side of the patient and the scrub nurse assisting during the operation. The energy tower and monitor were positioned at the patient's feet (Figure 2). Endoscopic vision and electrosurgery were provided by the standard endoscopic set available in the operating theatre.

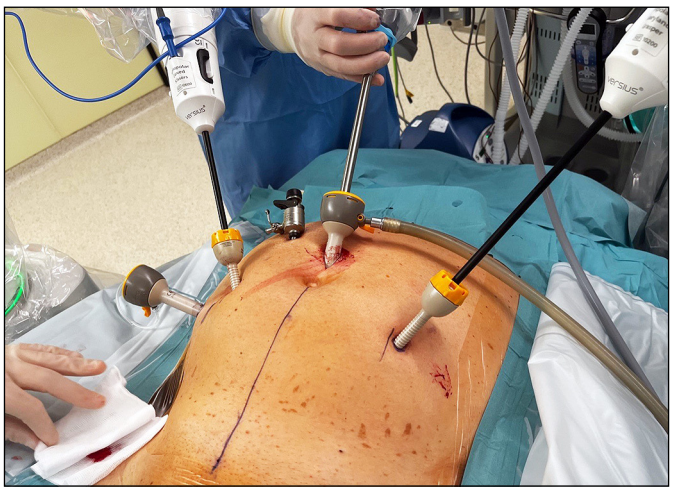

Figure 1. *Ports set up.*

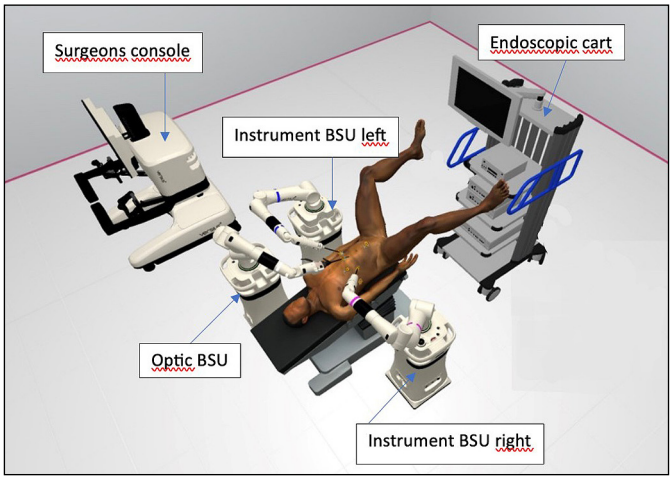

Figure 2. *System set up.*

BSU – bedside unit

Initially, the visual unit, positioned cranially on the left side of the patient, is docked. Camera mounting and port training are then performed. Subsequently, the 2 adjacent units are docked on both sides of the patient, caudally to the camera unit, as depicted in Figure 2.

During the operation, instruments are mounted, including a bipolar Maryland grasper on the left and monopolar curved scissors on the right. These instruments have a length of 30 cm and a diameter of 5 mm. Swipe and reach manoeuvres are performed to assess the range of operating tools for prostate excision and bilateral lymphadenectomy.

The scrub nurse worked on the right side of the patient, alongside the table assistant, to facilitate communication and access to the urethra. This configuration also allowed for easy access to all the robotic arms for instrument changes and camera cleaning.

RARP was performed in all cases using a transperitoneal anterior approach following standardized procedural steps [9]. The procedure began with bladder detachment, followed by incision of the endopelvic fascia and bladder neck dissection. Subsequently, dissection of the vas deferens and seminal vesicles was performed, followed by dissection of the posterior space between the prostate and rectum, dissection of the lateral parts of the prostate, suture of the dorsal venous complex, dissection of the prostate apex, posterior reconstruction, and vesicourethral anastomosis using 2 semi-continuous sutures. Each time, a leak test was conducted by filling the urinary bladder through the Foley catheter up to 100 ml. In cases where some leakage occurred, additional sutures were placed to secure it.

In all cases, a configuration of 3 robotic units was used, with a monopolar curved monopolar shear, a bipolar Maryland grasper, and a large needle driver. In cases where a fourth unit was used, it was placed caudally on the right side of the patient to accommodate a large fenestrated grasper, providing better exposure of the operating site.

The patients' data are presented in Table 1.

Complications, as per the Clavien-Dindo classification, were categorized as follows: Grade II complications occurred in 2 cases, and Grade III complications occurred in 4 cases. Additionally, one case required conversion to an open procedure, representing a 0.58% conversion rate. In this case, the decision to convert to an open procedure was necessitated by the presence of an inflammatory condition in the bladder resulting from prior BCG therapy, which rendered a safe resection of the prostate unfeasible.

Two cases of rectal damage were reported during the study. In the first case, the damage was identified and repaired during the surgery, obviating the need for a conversion to laparoscopic or open procedures. However, in the second case, rectal damage became evident 7 days after the operation. This damage was attributed to a Hem-o-Lock clip that had been placed on the rectal wall, leading to the development

Table 1. *Patients' preoperative and postoperative characteristics*

1	Number of patients	58
2	Median age (years)	66.9 (range 52–75)
3	median PSA (ng/ml)	9.8 (range 1.9–29.4)
4	ISUP ≥ 3 tumour on prostate biopsy	25/58 (48%)
5	MRI with a suspicion of extraprostatic disease	15/58 (25.8%)
6	Low risk prostate cancer	7/58 (12.06%)
7	Intermediate risk prostate cancer	40/58 (68.96%)
8	High risk prostate cancer	11/58 (18.9%)
9	Median console time (minutes)	150.9 (range 62–279)
10	Median operative time (minutes)	213 (range 128–348)
11	Extra prostatic disease on final pathology	27/58 (46.5%)
12	Positive surgical margins	15/58 (25.8 %)
13	Undetectable PSA (<0.1 ng/ml) 6 weeks after surgery	96.5 % (56/58)
14	Urinary continence after 6 weeks	52/58 (89.7%)
15	Median blood loss (ml)	437 (range 210–2050)
16	Complication rate	6/58 (10.3%)
17	Median hospital stay (days)	4.5 (range 4–12)
18	Median catheter duration (days)	7.9 (range 7–21)
19	Median prostate volume on preoperative MRI (cm^3)	48.5 (range 21–120)
20	Median BMI (kg/m^2)	27.3 (range 19–36)

ISUP – International Society of Urologic Pathology; MRI – magnetic resonance imaging; PSA – prostate-specific antigen; BMI – body mass index

of a urethro-rectal fistula. Fortunately, the fistula was successfully repaired endoscopically using the 'Endo Stitch' technique, which was performed with the aid of a colonoscope by gastroenterologists.

During the postoperative course, anastomotic leaks were observed in 3 cases, accounting for a 5.1% incidence. These leaks were confirmed by cystograms. The management approach involved conservative treatment, along with the prolonged maintenance of the Foley catheter and Redon drain in the abdominal cavity. Fortunately, all cases of anastomotic leaks resolved successfully.

The Versius robotic platform incorporates an advanced security control system with various event notifications and alarms designed to alert users to different types of improper events. We have categorized these events into 3 groups, each with a distinct impact on the operation. All events are recorded in real time and stored by the telemetric system. At the beginning of each operation, 3 BSUs (2 instrumental BSUs and 1 visualization BSU) are prepared and draped before the procedure, readily available close to the operating table if required.

1. Small events (clashes) are signalled by audible and visual notifications that do not significantly affect the progress of the procedure. These events are triggered by the following:
   - Collisions of the robotic arms
   - Collisions of the instruments with each other or with tissues
   - Excessive rotation of the instrument's wrist
   - Trocar angles that are too steep (phantom clash)
2. In addition to those small events, the Versius system also reports more critical improper events, categorized as MPAs (medium priority alarms). Those alarms are activated by excessive force on the robotic arm due to the following:
   - Dynamic collisions between robotic arms
   - Decreased abdominal insufflation
   - Inadvertent patient movement on the operating table (sliding caused by the Trendelenburg position)
   - Increased abdominal pressure due to insufficient muscle relaxation (anaesthesia-related)

MPAs necessitate a restart of the affected unit with a self-test (power-on self-test (POST)).

3. The most severe events – HPAs (High Priority Alarms) – lead to the exclusion of the affected BSU from the surgery. A BSU must be swapped under standard settings during the operation. In most cases, this involves one element of the platform (console, BSUs) not the entire system. This approach allows the operation to continue without interruption. BSUs not affected by an alarm can remain operational until the malfunction is fixed.

These major alarms demand immediate attention because they can significantly impact the proper functioning of the system and the surgical procedure. Given that the Versius robotic system is relatively new and continuously evolving, the team encountered several incidents, including both medium and major alarms, which were successfully resolved during its operation.

Table 2 presents all the above-mentioned data related to the performance of the Versius robotic platform. Figure 3 presents the number of minor incidents in relation to the number of procedures over time in our case series.

DISCUSSION

Prostate cancer stands as one of the most commonly diagnosed cancers in men globally, presenting a significant health challenge that necessitates a comprehensive approach, incorporating various treatment modalities including robotic prostatectomy. The objective of our study is to present and assess the outcomes of a group of 58 patients who underwent RARP due to prostate cancer, and to evaluate the performance of the Versius robotic system.

Table 2. *Versius system performance*

1. Small events (clashes)	1266 (range 3–107)
2. MPAs	14
3. HPAs	0
4. Instrument swaps (malfunction)	43 (range 1–6)
5. Console alarm	0
6. System failure	0

BSU – bedside unit; MPAs – medium priority alarms; HPAs – high priority alarms

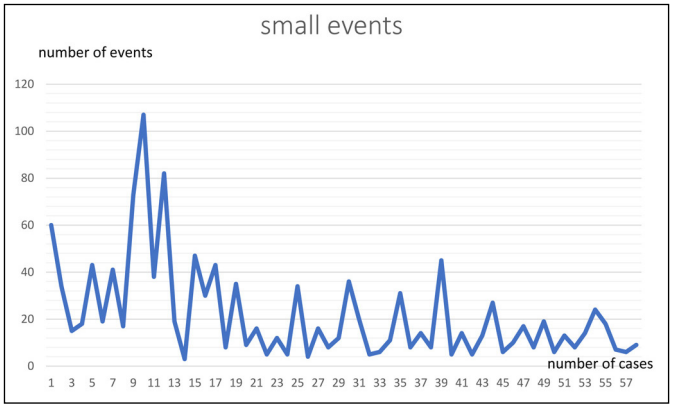

Figure 3. *The number of minor incidents in relation to the number of procedures over time.*

We retrospectively collected medical data for this patient group over a span of 6 months. The results and conclusions presented herein aim to offer insights into the performance and effectiveness of a urological team without prior experience in robotic surgery and into the performance of the new Versius robotic platform.

Our patient group comprised individuals across the same diverse risk factor categories as reported by other authors [10, 11]. This group includes 7 (12.06%) classified as low risk, who opted for RARP rather than active surveillance and underwent the RARP procedure. Furthermore, the data presented regarding early urinary continence after the procedure are consistent with findings in other publications [12].

The Versius system is one among several new robotic platforms available in the market alongside systems such as Hugo RAS, Hinotori, Avatera, and more, with the Da Vinci system being the most well-known and widely used [13]. Each platform offers its set of advantages and disadvantages. Ultimately, the choice of which platform to utilize depends on the specific surgical procedures, the preference of the surgeon, and the healthcare system in place.

All these robotic systems support various surgical procedures including prostate operations for benign prostate hyperplasia [14] and other urological procedures [15] not limited to RARP. They offer benefits such as enhanced precision with wrist-like instruments, precise control and stability of the surgical arms, and excellent 3D vision, making surgical procedures more comfortable to perform [16]. However, these may differ from one another in certain aspects, such as open or closed console design, hand or foot-controlled manipulators, instrument size, and combined or separated arms [17]. The features are important, but they do not greatly influence the general concept of the robot-assisted surgery. Unfortunately, all of them are very expensive, but we believe that the competition will reduce the prices and accelerate the technical progress. When comparing different robotic platforms, a major difference is the cost and affordability. The Da Vinci system is the most expensive [18], while Versius is designed to be more accessible and affordable [13]. This affordability makes the Versius system potentially more widely available, particularly for hospitals and healthcare systems in developing countries. The Hugo system falls between these 2 robotic systems, being somewhat expensive but designed with adaptability and flexibility in mind [19].

The CMR system we have introduced possesses several favourable characteristics worth mentioning. It is generally small and relatively lightweight, making it easy installable in nearly any operating room without requiring structural modifications. The independent arms enhance ease of docking, even in non-standard setup. The number of arms can be adjusted as per the case, and all components can be readily transported and stored within an operating room or hospital. Furthermore, it can be seamlessly integrated with available surgical devices in the operating theatre. Endoscopic vision and electrosurgery can be provided using the standard endoscopic tower-set, reducing costs. Our team used a standard Covidien laparoscopic set in a standard operating room without any structural adaptations.

The Versius instruments are also the smallest from those available on the market, with a diameter of 5 mm and shorter length of 30 cm [20]. The smaller incisions associated with these instruments can lead to reductions in pain, scarring, infections, and port site herniation. Additionally, the smaller instrument size facilitates conversion to laparoscopic surgery if necessary. However, the reduced instrument size may impact the strength of their jaws and their overall effectiveness, primarily for scissors and Maryland grasper. The company is actively working on improving these issues. [21]. One innovative feature of the Versius robotic platform is its modularity and small size, allowing for easy transport within the surgical theatre and the ability to use additional BSUs as needed. This flexibility empowers the surgeon to adapt to different patients and surgical scenarios, particularly in obese cases. The modularity and small size eliminate the need for special adaptations of the operating room, which is required for the larger Da Vinci system [22, 23].

Another feature under development is a robust security control system. This system proactively notifies personnel of situations where undesirable interactions between instruments and the patient's body may occur. It displays multiple types of alarms and can even halt the system when necessary. Some of the potential issues it detects include clashes between instruments, excessive force applied to tissues, lack of wrist rotation during manoeuvres, and other anomalies. These issues are usually solvable without interrupting the procedure, although there are also medium level alarms that can temporarily halt the operation until the problem is resolved. In rare cases, the highest level of alarms may be triggered by inadvertent changes in patient position, console malfunctions, or BSU malfunctions. When these alarms activate, the surgical team must promptly address and resolve the issues before the system can resume its work. While this robust security control

mechanism significantly enhances patient safety, there have been occasional concerns about minor alarms causing brief delays in surgery. Consequently, the company is diligently analysing and refining the system to optimize its performance.

Another characteristic of the Versius robot is its constant online telemonitoring capability. This feature primarily aims to facilitate technical service supervision, ensuring the system operates smoothly. It also presents opportunities for data recording.

The recorded data can have numerous implications, such as enhancing surgical training, evaluation, and certification processes.

It is essential to emphasize that all the mentioned features of complex surgical tools like the Versius robot, as well as other surgical robots, must undergo thorough exploration before implementation. This exploration is achieved through comprehensive training programs provided by the companies, which typically include virtual simulations, cadaveric exercises, and supervised stages to ensure that surgical teams are well-prepared and competent in operating the robotic systems effectively and safely.

CONCLUSIONS

Our team successfully initiated a robotic surgery program using the Versius robotic system. We believe that our shared experience can offer valuable insights into what a new, inexperienced robotic team can expect when beginning to use the Versius system and what surgical results can be achieved, particularly as there are not many reports on the RARP procedure with the Versius. The key message is that the implementation can be quick and effective, provided that all necessary teaching steps are fulfilled.

The system has its specific characteristics, but the overall concept of robotic surgery resembles the better known DaVinci platform, with its own advantages and drawbacks. We anticipate that competition will drive the development of all these systems.

Further studies and comparative analyses are required to evaluate the clinical outcomes and cost-effectiveness of this technology.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

UROLOGICAL ONCOLOGY

First worldwide report on safety and efficacy of using small 7.5 Fr scope for pediatric ureteroscopy: prospective pilot series from Europe

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Introduction Although pediatric urolithiasis remains relatively uncommon, its global prevalence is on the rise. Technological advances have led to miniaturization of instruments especially in the form of single use scopes. As the evidence on the use of small single use ureteroscopes in children is scarce, we have conducted a pilot two-center study to analyze the outcomes of pediatric patients treated with the Pusen 7.5 Fr single use scopes at our institutions.

Material and methods This study included consecutive pediatric patients with urinary stones treated with the small Pusen 7.5 Fr single use ureteroscope. The study was conducted at two large European tertiary endourology centers that specialize in pediatric kidney stone management. Patient data and outcomes were prospectively collected, and analysis was performed regarding patient demographics, stone parameters, as well as stone free rate (SFR), operating time, and complications.

Results In this pilot study, 26 patients were included with a median age of 12 years (7.0–16.0) and a male to female ratio of 14:12. The mean cumulative stone size was 15.15 mm (SD ±11.1) and multiple stones were present in 9 (34.6%) patients. Pre-operative stent, access sheath and post-operative stent usage was done in 12 (46.2%), 23 (88.5%) and 13 (50%) patients respectively. The median operative time was 47 minutes (IQR: 40.0–63.8). Following the initial procedure 24 (92.3%) patients were stone free, while no intra or postoperative complications were observed.

Conclusions Our study demonstrates that the use of the small 7.5 single use ureteroscope is safe and efficient for the treatment of urinary stones in pediatric patients with high stone-free rates and no complications noted in our series. While this might become a standard of care in future, to confirm and validate our findings further studies with larger cohorts are warranted.

Key Words: paediatric ‹› children ‹› ureteroscopy ‹› pusen ‹› kidney calculi ‹› single use ureteroscope

INTRODUCTION

There has been a notable rise in pediatric stone disease in the recent years. This is probably attributed to shifts in dietary habits and increased sedentary behaviors [1]. The upward trend has resulted in a worldwide incidence of as much as 15%, depending on the region and epidemiological data [1, 2]. In terms of gender, it's more prevalent in males during their first ten years of life compared to females in their second decade. Notably, research indicates that the most significant increase has been among

teenage girls [3]. About one third of pediatric patients who present with stone disease might need surgery. Pediatric urolithiasis tends to recur, often linked with metabolic or anatomical anomalies or infections [4, 5, 6]. Given the high possibility of symptoms reappearing (up to 50% within three years), it's crucial to offer treatments that are both highly effective and have minimal side effects [7]. As a result, there's an increasing need on minimally invasive treatment methods, including shockwave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL) and ureteroscopy (URS).

Technological advances have led to miniaturization of instruments especially in single use scopes. These smaller single use digital scopes seem to be advantageous especially in cases with difficult access to the renal pelvis due to challenging anatomy and might therefore be translating into successful endoscopic stone treatment in children [8]. As the evidence on the use of single use ureteroscopes in children is scarce, we have conducted a pilot two-center study to analyze the outcomes of pediatric patients treated with the 7.5 Fr single use ureteroscopes at our institutions.

MATERIAL AND METHODS

Study design and patient selection

This study included consecutive pediatric patients with urinary stones treated with the Uscope 7.5 Fr single use digital ureteroscope (Pusen Ltd., Zhuhai, China). The study was conducted at two large European tertiary endourology centers that specialize in pediatric kidney stone management: Fundació Puigvert, Barcelona Spain and the University Hospital Southampton NHS Trust, Southampton, UK. The study was officially registered as an audit within the respective hospitals. A retrospective analysis of prospectively collected data was performed. Patient demographics, stone location, single and cumulative size, composition, stone-free rates (SFR), operating time, pre and postoperative stent and peri/postoperative complications were documented over two years (December 2021-June 2023).

Preoperative non-contrast CT (CTKUB) or Ultrasound scan (USKUB) was performed for diagnostic imaging. Patients with positive pre-operative urine culture received appropriate treatment based on sensitivity analysis.

Surgical technique

At both centers the procedures were performed by an experienced surgeon. After an initial cystoscopy, placement of safety wire and a rigid URS was performed using a 4.5 Fr Wolf or Storz semi-rigid ureteroscope. The Uscope 7.5 Fr single use ureteroscope (Pusen Ltd., Zhuhai, China) was used for flexible ureteroscopy. A ureteral access sheath (UAS) was placed at the surgeon's appraisal (9.5 F/11.5 F Cook Flexor UAS). Laser lithotripsy was performed with Holmium:YAG or a Thulium super fiber laser and a 150-275 μm laser fibre was used for laser lithotripsy.

The laser settings were maintained at 0.4–1J and 5–50Hz, utilizing fragmenting, dusting and pop-dusting techniques. Fragments were extracted using a nitinol basket (Ngage, Cook Medical, Bloomington, IN, USA or Dakota, Boston Scientific Corporation). A 4.8F or 6F ureteral stent was inserted postoperatively if deemed necessary (example – planned second look, long procedural time or use of UAS). Stone free rate (SFR) was defined as endoscopically stone free and <2 mm fragments on postoperative imaging, which was a plain X-ray or CT scan, or USS at 4–6 weeks post-surgery. Complications were assessed according to the Clavien–Dindo classification system.

Data was collected using Microsoft Excel 2016 (Microsoft, Redmond, WA, USA). Statistical analysis was conducted using SPSS version 26 (IBM, Armonk, NY, USA).

RESULTS

Patient characteristics

In this study, 26 consecutive patients were included, with a median age of 12 years (IQR: 7.0–16.0). The male-to-female ratio was 14:12 (Table 1).

Stone characteristics

The mean cumulative stone size was 15.51 mm (SD ±11.1), and multiple stones were present in 9 (34.6%) patients. Stone locations varied, with notable occurrences in the mid-pole (10 patients) and lower pole (8 patients). Partial staghorn stones were found in 2 patients. Stone composition analysis revealed various stone types, including calcium oxalate monohydrate, calcium oxalate dihydrate, calcium phosphate carbonate, magnesium ammonium phosphate hexahydrate, amorphous calcium phosphate carbonate, and brushite.

Treatment outcomes

Preoperatively, 12 (46.2%) patients had stents in place. A UAS was used in 23 (88.5%) cases during

Table 1. *Patient demographics, stone characteristics and outcomes*

Overall (n = 26)	Results
Age (median, IQR)	12 (7.0 – 16.0)
Male	14 (53.8%)
Female	12 (46.2%)
BMI	18.3 (16.7– 23.5)
Stone location	
Pelvis	5
Upper pole	5
Mid pole	10
Lower pole	8
Partial staghorn	2
PUJ	3
Ureter	1
Stone composition	
Calcium oxalate monohydrate	17
Calcium oxalate dihydrate	8
Calcium phosphate carbonate	16
Magnesium ammonium phosphate hexahydrate	5
Amorphous calcium phosphate carbonate	1
Brushite	1
Multiple stones	9 (34.6%)
Total stone length in mm (mean, SD)	15.15 ±11.103
Pre-operative stent	12 (46.2%)
Operative time in min (median, IQR)	47 (40.0–63.8)
Ureteral access sheath	23 (88.4%)
Post-operative stent	13 (50%)
Complications	0
Stone-free	24 (92.3%)

BMI – body mass index; IQR – interquartile range; SD – standard deviation

the procedures. Postoperative stents were inserted in 13 (50%) patients. The median operative time was 47 minutes (IQR: 40.0–63.8). Following the initial procedure, 24 (92.3%) patients were stone-free. No intra or postoperative complications were observed.

DISCUSSION

The miniaturization of surgical instruments and the introduction of flexible ureteroscopes have made it possible to treat urinary stones in children endoscopically throughout the whole urinary tract. Whereas in the past only lower ureteral stones were treated with semirigid ureteroscopy, and extracorporeal shock wave lithotripsy (SWL) was the primary treatment method for kidney stones up to 2 cm in pediatric cases [9]. SWL's effectiveness, however, diminishes notably with the growth in stone size and number [10]. Often multiple sessions are required to reach stone free status which can first be reached after a couple of weeks after SWL treatment [11]. For bigger stones percutaneous nephrolithotomy is a viable treatment option with higher SFR after a single procedure [12], however it bears the risk of major complications such as bleeding or kidney injury [13].

In recent years retrograde intrarenal surgery (RIRS) has emerged as a practical and noteworthy treatment option. In comparison to SWL, RIRS has a higher SFR but demands a longer surgical duration and hospitalization [14]. Compared to PCNL in treating extensive stones, RIRS has a lower SFR. However, in terms of overall effectiveness, both RIRS and PCNL showcase comparable SFR [15, 16]. The growing accessibility and miniaturization of endourological instruments has enabled the endoscopic management of urinary stones in pediatric patients [9]. These advancements have partly come in the form of single-use flexible ureteroscopes such as Uscope 7.5 Fr (Pusen Ltd., Zhuhai, China) [17]. The smaller single-use scopes may offer advantages in cases with difficult anatomy and therefore reduce the risk of ureteric and scope damage, and especially useful in cases of multi resistant urinary infection [18].

Our study demonstrates that RIRS with the Uscope 7.5Fr single use scope is a safe and efficient treatment option for urinary stones in pediatric patients with a stone free rate of 92.3% after the first procedure and no intra or perioperative complications. For both patients in whom stone free status could not be achieved after the first procedure the total stone length was >35 mm (56 and 35 mm) and a staged procedure was planned after parental counselling.

A preoperative stent was placed in 46.2% of patients. However, some of the patients initially presented at centers not specialized for pediatric stone surgery, where they were initially stented and then referred to our centers for the final stone treatment. While in a UAS was used in 88.4% of the patients a postoperative stent was inserted in only 50% of the patients. The use of smaller ureteroscopes allows for the use of smaller UAS with the same effect, since the cross-sectional space between the UAS and the scope and therefore the space for fluid outflow remains nearly the same. Although the use of UAS has proven safe and can lead to a reduction of intrarenal pressure and temperature in children, there still is the concern of ureteric injury [19, 20, 21]. The use of smaller UAS leads to a lower rate of ureteric injuries [19, 22] and might lead to less need of post operative stent placement.

While this study is the first study to report outcomes of endoscopic stone treatment pediatric patients with a 7.5 Fr single use flexible ureteroscope and was carried out in high volume endourology centers with data retrieved for consecutive patients, it was

a small pilot study. Larger prospective studies with standardized outcomes are warranted to validate our findings in addition to having long-term follow-up to look at relevant outcomes. Previous French study in paediatric age group shows the advantage and cost-effectiveness of single use scope compared to reusable scopes [23]. Efforts must therefore be done to balance the cost of using scopes and consumables which are best suited for the given healthcare [24] With centers now pushing for ureteroscopic treatment for larger stones [25], and advent of newer lasers [26], smaller sized ureteroscopes are going to further enhance this technique [27], giving a stiff competition for percutaneous techniques [28].
Furthermore, SFR was, in most cases, assessed with non−CT modalities acknowledging that this could have overestimated the SFR. However, we deemed the use of additional radiation and therefore CT scans was not justifiable in our pediatric patient cohort.

CONCLUSIONS

Our study demonstrates that the use of the smaller 7.5Fr single use ureteroscope is safe and efficient for the treatment of urinary stones in pediatric patients with high stone-free rates and no complications noted in our series. While this might become a standard of care in future, to confirm and validate our findings further studies with larger cohorts are warranted.

CONFLICTS OF INTEREST

BS is a consultant for Pusen, but the company has had no involvement in the study or data collection or analysis. No other external influence was there for this study.

ETHICS

The study was registered as an audit/study in the respective hospitals and parents were consented for the study.

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REVIEW PAPER

FUNCTIONAL UROLOGY

Traditional and innovative interventions in the management of enuresis

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Introduction Enuresis (NE) is a socially stigmatising and stressful condition affecting children's and parent's quality of life. The aim of this review was to evaluate and summarize the current knowledge about the pharmacological and non-pharmacological traditional and innovative treatments in children with NE.
Material and methods We examined the following bibliographic electronic databases: PubMed and the Cochrane Library, from January 2000 until July 2023. The search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (8) and was limited to English-language papers that focused on enuresis in patients under 18 years old. Each paper that met the eligibility criteria was reviewed and analyzed in full text by three authors and any discrepancies among them were solved by debate. Due to the heterogeneity of the articles examined, we focused on a qualitative analysis.
Results Overall, we identified 560 records through database searching. As first step, we excluded 46 articles in non-English language, 6 records whose related articles were not available, 8 articles concerning ongoing trials and 210 duplicated papers. As second step, we eliminated 215 records by evaluating only title and abstract because they did not match the inclusive criteria we mentioned before. Of the remaining 75 studies, we excluded 34 through a further discussion among authors upon the reliability of data. Thus, 41 selected articles were included in the review.
Conclusions Multiple treatment approaches, both pharmacological and non pharmacological, have been established and validated to reduce signs and symptoms of NE and improve quality of life and the social and emotional discomfort experienced by children. The aim of pediatrician is to identify the right therapy protocol for very single child, evaluating the best approach for him and the family.

Key Words: enuresis ‹› management ‹› treatments

INTRODUCTION

Enuresis (NE) is a socially stigmatising and stressful condition affecting children's and parents' quality of life. According to the International Children's Continence Society (ICCS), NE is defined as a non-voluntary intermittent bedwetting while sleeping in children, especially aged 5 years or more, and more frequent in males (the male:female ratio is 3:1) [1]. The prevalence of NE is variable: it is above 10% among 6-year-olds, around 5% among 10-year-olds, and 0.5–1% among teenagers and young adults [2, 3]. NE is subdivided into primary and secondary variants. Primary NE, the most common type, occurs when the child has never experienced a period of nighttime dryness lasting longer than 6 months, while secondary NE occurs when nonvoluntary discharge of urine returns after at least a 6-month pe-

riod of nighttime dryness. The underlying causes of these 2 conditions are different: primary NE is the result of the simultaneous presence of several factors such as the failure to arouse from sleep despite receiving stimuli combined with either excessive urine production, small capacity of the bladder, or the detrusor overactivity. The increased arousal thresholds do not, however, mean that these children sleep well; in fact, sleep quality among enuretic children is often poor [4, 5]. There is also a genetic predisposition to primary NE, probably involving chromosomes 12, 13, and 21; this is confirmed by the increased incidence of this disease in children whose parents suffered from it. The incidence is about 15% in children whose parents did not experience NE, 44% in children with only one parent who suffered from it, and 77% if both parents experienced NE [6]. Secondary NE is caused by either the new onset of a medical condition, such as urinary infection, hypothyroidism, renal disease, obstructive sleep apnoea, diabetes insipidus, diabetes mellitus, or by a new psychological stress. Another important clinical classification divided NE into monosymptomatic (MNE) and non-monosymptomatic enuresis (NMNE): the latter term is reserved for those children who, in addition to their bedwetting, have daytime lower urinary tract symptoms (LUTS) such as urgency, daytime incontinence, voiding difficulties, and altered daytime voiding frequency. Many pharmacological and non-pharmacological approaches have been proposed in the management of NE, the treatment of which depends on coexisting disorders, the subtype of enuresis (MNE or NMNE), the severity of the problem, the child's motivation, and the compliance of their parents [7]. While the treatment of secondary NE coincides with the treatment of the underlying medical condition that causes it, the first-line treatments for primary NE are drugs (especially desmopressin in MNE and anticholinergics in NMNE) and behavioural protocols. The aim of this review was to evaluate and summarize the current knowledge about the pharmacological and non-pharmacological traditional and innovative treatments in children with NE.

MATERIAL AND METHODS

We examined the PubMed and the Cochrane Library bibliographic electronic databases from January 2000 until July 2023. The search was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [8] and was limited to English-language papers that focused on enuresis in patients under 18 years old. To be considered eligible for the review, papers had to include the following components: 1. subjects (children) with diagnosis of enuresis; 2. who received pharmacological and non-pharmacological approaches as treatment; 3. clinical outcomes evaluated in short- and long-term period. We excluded: non-English-language papers and studies in which clinical outcomes were not evaluated or were not statistically significant. The key words used for the search across electronic databases were as follows: 'enuresis' or 'nocturnal enuresis' or 'bed-wetting' and 'pharmacological treatment' or 'drugs' or 'desmopressin' or 'oxybutynin' or 'anticholinergics' or 'imipramine' or 'mirabegron' or 'non-pharmacological treatment' or 'alarm' or 'dietary' or 'pelvic floor training' or 'bladder advice' or 'hypnosis' or 'acupuncture' or 'comorbidity'. The abstracts of the papers were assessed by a single reviewer (PF), who strictly applied the inclusion/exclusion criteria mentioned above to decide whether a paper was eligible for full review. Each paper that met the eligibility criteria was reviewed and analysed in full text by 3 authors (PF, IC, and MZ), and any discrepancies between them were solved by debate. Due to the heterogeneity of the articles examined, we focused on a qualitative analysis (Figure 1).

Data extraction and ethics statements

The data extracted from each eligible paper included the following: study design, study population characteristics, type of treatment, and clinical outcomes. In this review, we analysed the current literature on the main pharmacological and non-pharmacological treatment in children with enuresis. Thus, ethical approval was not required.

RESULTS

Overall, we identified 560 records through database searching. As a first step, we excluded 46 articles in non-English language, 6 records whose related articles were not available, 8 articles con-cerning ongoing trials and 210 duplicated papers. As a second step, we eliminated 215 records by evaluating only title and abstract because they did not match the inclusive criteria we mentioned before. Of the remaining 75 studies, we excluded 34 through a further discussion among the authors upon the reliability of data. Thus, 41 selected articles were included in the review. The detailed selection of the literature is shown in Figure 1. The characteristics of all included studies are summarised in Table 1 and Table 2.

Pharmacological treatment

Many pharmacological treatments have been studied for NE, and both desmopressin and anticholinergics

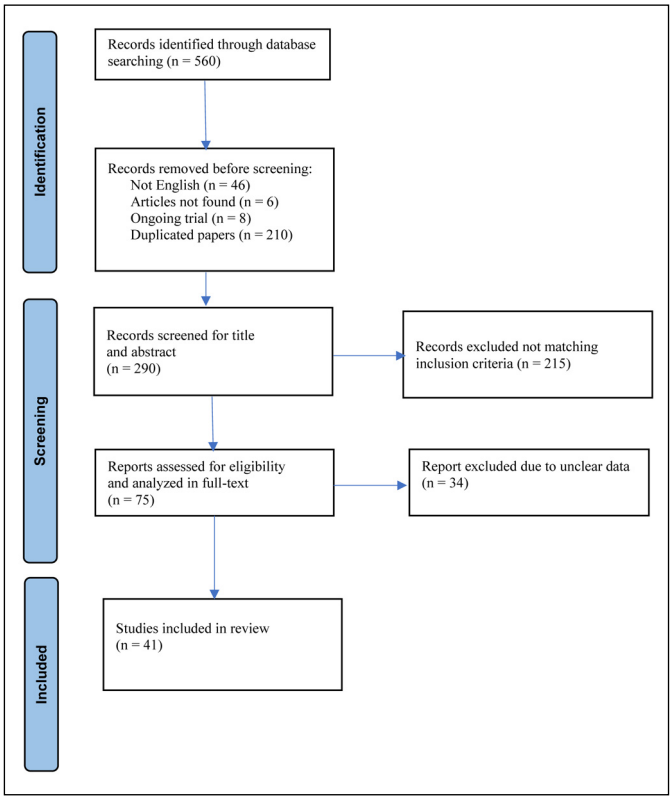

Figure 1. *The detailed summary of the literature search.*

are the main drugs used nowadays by paediatricians as a first-line approach.

Desmopressin (dDAVP) is considered the first-line treatment for children who do not respond to behavioural interventions alone or for those who need an immediate response (for example in the case of sleeping away from home) [1]. It is an analogue of the antidiuretic human hormone vasopressin (or antidiuretic hormone): it acts by increasing the reabsorption of fluid from the renal tubules and decreasing urine production. About 80% of children subjected to dDAVP have a good response rate but with a high incidence of recurrence at the end of the therapy. For example, Kwak et al. in a randomized controlled trial showed that 77.8% of the desmopressin group achieved a successful result, but about 50% experienced a relapse when treatment stopped [9]. Van Herzeele et al. and Kruse et al. evaluated possible predictive factors to desmopressin response, and they demonstrated that desmopressin response rates were higher in children with greater age, while Dehoorne et al. showed that nocturnal polyuria as an isolated factor cannot dependably predict a desmopressin response, even if the functional bladder capacity is also considered [10, 11, 12]. Bladder structural and functional features have been evaluated in children subjected to desmopressin therapy. Hamano et al. found that desmopressin was less effective in children with a low functional bladder capacity, and Montaldo et al. suggested the use of anticholinergic agents for a subset of children with enuresis, who had a restricted bladder capacity and thickened bladder wall [13, 14]. Hara et al. conducted a molecular investigation documenting urinary aquaporin 2 as a biomarker of the effectiveness of desmopressin treatment during therapy, and plasma copeptin levels before treatment as a predictor factor of desmopressin response [15]. Desmopressin must be taken 1 hour before going to sleep and its intake should be implemented with a reduction in fluid intake for the following 8 hours [16]. It is available in oral tablets, in doses of 0.2–0.4 mg, and oral quick-melting lyophilizate (MELT), available in doses 60–120–240 μg. Two therapy protocols have been proposed: starting with the full dose and titrating down after a week/in the case of good treatment effect or starting with the lower dose and increasing until the response dose. In either case, the efficacy is usually immediately evident and there is no recommendation for prolonged medication for more than 2 weeks in a child who shows no beneficial effects [17]. Even if the safety of both formulations has been assessed, it seems that the clinical efficacy and pharmacological properties of the MELT formulation are superior to those of tablets. Juul et al. and Schulz-Jurgensen et al. found that desmopressin MELT, compared with the tablet, improved the probability of being a responder, and that switching from tablet to MELT formulation increased patient compliance, which was associated with increased efficacy [18, 19]. Moreover, while there is consensus that therapy with dDAVP tablets should be discontinued in a structured withdrawal program, Ferrara et al. demonstrated that a structured withdrawal program from MELT therapy does not offer advantages compared to an abrupt termination [20, 21]. Vande Walle et al. conducted a clinical trial to determine the pharmacodynamic properties of oral lyophilizate formulation of desmopressin and to identify the dosages that could provide a duration of action corresponding to a typical length of night-time sleep in children with NE. They found that a small dose range (120–240 μg) is likely to control diuresis for a period corresponding to a night's sleep in most children even if some patients required a higher dose to obtain antidiuresis for the complete night [22]. Lottmann et al. in an open-label, randomised, cross-over study evaluated the preference of children and adolescents with NE for vs. tablet treatment. They registered a high preference for MELT formulation with similar levels of efficacy and safety at lower doses than those of the tablet [23]. Desmopressin can be

Table 1. *Pharmacological treatments*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Kwak et al. (2010)	Randomized controlled trial	104 children with MNE	8.1 (desmopressin group) 8.6 (enuresis alarm group)	Group desmopressin 45 boys 9 girls Group enuresis alarm 34 boys 16 girls	54 desmopressin 50 enuresis alarm	Successful result in 77.8% of the desmopressin group and 82% of the enuresis alarm group Full response in 37% and 50% of the two groups Relapse in 50% of the desmopressin group and 12% of the enuresis alarm group
Kruse et al. (2001)	Clinical trial	399 children with primary NE	Not mentio-ned	295 boys 104 girls	Desmopressin	134 of the responders (71%) needed 40 mg desmopressin 29 (59%) of the full responders needed 20 mg
Dehoorne et al. (2007)	Clinical trial	125 children with MNE subdivided into 2 Groups (63 full responders and 62 nonfull responders)	Full responders: 9.9 Nonfull responders: 8.7	Full responders: 45 boys 18 girls Nonfull responders: 39 boys 23 girls	Desmopressin	No differences in pretreatment values of functional bladder capacity, circadian rhythm of urine production or urine osmolality were found between desmopressin full responders and nonfull responders.
Hamano et al. (2000)	Clinical trial	114 children with MNE	9.3	88 boys 26 girls	Desmopressin and retention control training (RCT)	Improvement of 38.9% of desmopressin children vs 23.3% of RCT children In the DDAVP group, the functional bladder capacities at baseline in responders and nonresponders were 82 ±22% and 56 ±20% of the predicted bladder capacity
Montaldo et al. (2012)	Randomized controlled trial	206 children with MNE	10.6 ±2.9	117 boys 89 girls	Desmopressin plus oxybutynin	No difference between the 120 µg and 240 µg patients Higher rate of full and partial responses (45% success) in the desmopressin plus oxybutinin group Lower bladder volume and wall thickness index in responders to desmopressin plus oxybutinin
Hara et al. (2017)	Clinical trial	32 children with NE and polyuria	8.1	23 boys 9 girls	Desmopressin	After 8 weeks of treatment significant correlation between day/night ratio of aquaporin 2 and percentage of wet nights. In responders there was a significant difference in the change in aquaporin 2 day/night ratio from before treatment to complete remission For plasma copeptin the baseline day/night ratio for responders at 120 µg was significantly lower than in the 240 µg nonresponder group
Juul et al. (2013)	Randomized controlled trial	221 children with NE	9.6 ±2.4	158 boys 63 girls	Desmopressin	Greater probability of having an amelioration for de-smopressin melt compared with desmopressin tablet (OR = 2; 95 % CI, 1.07–3.73). The dose of desmopressin also significantly increased the probability of amelioration, with an OR of 3.05 favouring the lower dose melt 120 µg/tablet (0.2 mg) compared with the higher dose melt 240 µg/tablet (0.4 mg)
Schulz-Jürgensen et al. (2016)	Randomized controlled trial	134 children with NE	Not mentioned	Not mentioned	Desmopressin	Less difficulties in taking the medication and forgotten doses, higher treatent satisfaction and greater reduction in wet nights with the melt than with the tablet formulation
Ferrara et al. (2014)	Randomized controlled trial	81 children	8.64	Not mentio-ned	Desmopressin	47/81 (58.02%) responded to therapy 24/47 (51.06%) were randomly assigned to withdraw suddenly and 23/47 (48.94%) to withdraw gradually. One month after the end of treatment, relapse occurred in 11/23 (47.83%) of the structured withdrawal program group and in 11/24 (45.83%) of the abrupt termination group

Table 1. *Continued*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Vande Walle et al. (2006)	Randomized controlled trial	72 children with primary NE	Not mentioned	Not mentioned	Desmopressin	Mean duration of action of desmopressin at the lowest osmolality threshold level was 3.6–10.6 h, according to dose; for the highest threshold, the values were 1.3–8.6 h.
Lottmann et al. (2007)	Randomized controlled trial	221 children with NE	9.6 ±2.4	156 boys 65 girls	Desmopressin	56% preferred the MELT formulation Efficacy similar for both formulations (MELT: 1.88 ±1.94 bedwetting episodes/week; tablet: 1.90 ±1.85 episodes/week) Compliance was 94.5% for MELT patients vs. 88.9% for the tablet
Ravanshad et al. (2019)	Randomized controlled trial	40 children with NE	Not mentioned	Not mentioned	Desmopressin plus imipramine	Better recovery in 18 of 20 patients treated with combination therapy after 1 month with higher frequency of recovery (83.3%)
Kim et al. (2021)	Observational study	103 children with idiopathic overactive bladder	Not mentioned	Not mentioned	Mirabegron and solifenacin	The age-adjusted bladder capacity ratio increased from 0.71 to 0.96 ($p < 0.001$) and from 0.57 to 0.97 ($p = 0.002$) after solifenacin and mirabegron use, respectively. Decreased bladder capacity before medication was associated with responding to medication (odds ratio, 7.41; $p = 0.044$)
Esteghamati et al. (2023)	Randomized controlled trial	40 children with MNE and NMNE desmopressin-resistant	Not mentioned	Not mentioned	Desmopressin plus tolterodine Desmopressin plus indomethacin	Mean (SD) percent in NE reduction was: 1 month 58.86 (7.27)% vs 31.18 (3.85)% 3 months 69.78 (5.99) % vs 38.56 (3.31)% 5 months 84.84(6.21) % vs 39.14 (3.63) %; At 5 months, complete response to treatment was only observed with D+T, while treatment failure was significantly higher with D+I (50% vs 20%)
Kamperis et al. (2016)	Randomized controlled trial	23 children with MNE, nocturnal polyuria, and partial or no response to desmopressin	9.1 ±2.3	19 boys 4 girls	Desmopressin plus indomethacin	The addition of indomethacin to desmopressin significantly reduced nocturnal urine output (from 324 ±14 ml to 258 ±13 ml, $p < 0.001$). This did not lead to more dry nights in all children, and we found no statistically significant reduction in enuresis frequency (from 68% ±0.1 to 56% ±0.1, $p = 0.24$).
Ghanavati et al. (2021)	Randomized controlled trial	62 children with NE	8.70	Not mentioned	Solifenacin plus desmopressin Tolterodine plus desmopressin Desmopressin	Desmopressin plus solifenacin 19 of 20 patients (95%) achieved complete remission Desmopressin 14 of 22 patients (63.63%) achieved complete remission Desmopressin plus tolterodine 17 of 20 patients (85%) had complete remission
Austin et al. (2008)	Randomized controlled trial	34 children with NE refractory to the maximal dosage of desmopressin	10.50	24 boys 10 girls	Desmopressin plus anticholinergic medication	Long-acting tolterodine group had a higher rate of full and partial responses (44% success), compared with the placebo group (31% success). Larger proportion of patients who exhibited a complete lack of response (0% change) in the placebo group (44%), compared with the longacting tolterodine group (16.5%)
Lee et al. (2005)	Clinical trial	145 children with NE	7.8	100 boys 45 girls	Desmopressin Imipramine Desmopressin plus oxybutynin	Frequency of nocturnal enuresis before and after 6 months of treatment Combination therapy from 13.3 ±3.4 to 3.7 ±5.4 Desmopressin from 12.0 ±3.5 to 4.0 ±4.6 Imipramine from 13.2 ±2.9 to 9.3 ±8.3

Table 2. *Non-pharmacological treatments*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Van Leerdam et al. (2004)	Clinical trial	37 children (group 1) with NMNE 37 children (group 2) with MNE	7.7 (group 1) 7.8 (group 2)	Group I 25 boys 12 girls Group II 21 boys 16 girls	Alarm treatment	Group I: 65% became dry at night and 38% became dry during the day Group II: 75% became dry
Ozgür. et al. (2009)	Clinical trial	40 children with MNE	8.1	Not mentioned	Alarm treatment	Positive outcome in 27 patients with a full response in long-term follow-up (response rate 32.5%)
Taneli et al. (2004)	Clinical trial	28 children with MNE	Not mentioned	Not mentioned	Alarm treatment	The pre- and post-treatment maximum functional bladder capacity was 178.35 ±87.86 ml and 243.03 ±102.84 ml, respectively and the pre- and post-treatment mean day-time bladder capacity was 111.11 ±45.87 and 148.445 ±7.68 ml. The maximum nocturnal bladder capacity was found to be increased from 177.85 ±84.95 to 255.25 ±124.52 ml
Butler et al. (2007)	Clinical trial	12 children with NE	8.75	6 boys 6 girls	Alarm treatment	4 children (AVP responders) became dry, with concomitant increases in both mean corrected AVP (12.2 pg/min/Cosm pre-treatment vs 45.5 pg/min/Cosm post-treatment) and mean osmolality (480 mmol/kg pre-treatment vs 800 mmol/kg post-treatment). 4 children (AVP non-responders) showed an evident increase in mean osmolality (690 mmol/kg pre-treatment vs 890 mmol/kg post-treatment)
Kirill V Kosilov et al. (2018)	Randomized controlled trial	455 children with MNE	11.4	294 boys 161 girls	Alarm treatment Group A (n = 139) 12 weeks Group B (n = 136) 16 weeks Group C (n = 139) 20 weeks.	Success rate higher in groups B (80.7%) and C (85.5%) than in group A (67.4%) with no statistically significant difference between groups B and C
Tsuji et al. (2018)	Clinical trial	78 children with MNE	9.2	48 boys 30 girls	Alarm treatment in family assisted group (44) and alarm control group (34)	Full response and partial response in 36.4% and 20.5% in the family assisted group, and 26.5% and 29.4% in the alarm control group
Naitoh et al. (2005)	Clinical trial	105 children with MNE	9.4	76 boys 29 girls	37 alarm monotherapy 35 desmopressin with an alarm 33 imipramine with an alarm	Improvement rate of 80% in the desmopressin group and 79% in the imipramine group and 59% rate in the monotherapy group. No relapse in the monotherapy group
Ferrara et al. (2015)	Clinical study	137 children with MNE	Not mentio-ned	102 boys 35 girls	67 desmopressin and dietary advices (group A) 70 only desmopressin (group B)	Higher response rate and a lower number of relapse in group A vs group B with 67.2% of responders in group A vs 58.6% in group B, after 3 months of therapy and 31.1% of relapse in group A vs 46.3% in group B one month after the end of treatment
Campos et al. (2019)	Randomized controlled trial	38 children with NE	Group I 9.5 Group II 7 Group III 8	17 boys 21 girls	Group I standard urotherapy Group II standard urotherapy associated with pelvic floor training Group III standard urotherapy associated with pelvic floor training and oxybutynin	Complete success after 12 weeks: Group I: 58% Group II: 73% Group III: 55% Complete success after 2 years: Group I: 63% Group II: 75% Group III: 60%

Table 2. *Continued*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Vesna et al. (2011)	Randomized Controlled Trial	86 children with NE	7.1	Not mentioned	Group A diaphragmatic breathing exercises and pelvic floor retraining in addition to standard urotherapy Group B only standard urotherapy.	Urinary incontinence and nocturnal enuresis were cured in a significantly larger number of children in group A than in group B. Bell shaped uroflowmetry curve was observed in 36 patients in group A and only 4 children in group B.
Van Kampen et al. (2009)	Randomized Controlled Trial	63 children with NE	Not mentioned	Not mentioned	Experimental group (32) full spectrum therapy with pelvic floor muscle training Control group (31) Full spectrum therapy without training	No significant difference in treatment outcome, duration, maximal voided volume and relapse between the 2 groups. 89% became dry within 6 months. During the year after treatment 33.3% and 37.9% of the experimental and control groups relapsed, while the relapse rate at 1 year was 7.4% and 20.7%, respectively.
Garcia-Fernandez et al. (2020)	Randomized Controlled Trial	48 children with NE	7.6 ±2.5	14 boys 34 girls	Squatting exercises	41/48 children were cured of both daytime/night--time enuresis. A total of 32 (68%) children with constipation 92% cured; 9 (19%) soiling (all cured).
Zivkovic et al. (2012)	Randomized controlled trial	43 children with NE and urinary incontinence	7.5	15 boys 28 girls	Standard urotherapy plus diaphragmatic breathing and pelvic floor exercises	After one year of therapy, urinary incontinence was cured in 20/24 (83%), nocturnal enuresis in 12/19 children (63%), while 13/19 children (68%) were UTI free. Bell-shaped curve was observed in 36/43 children
Tkaczyk et al. (2017)	Prospective interventional multicenter trial	49 children with MNE	7.2	36 boys 13 girls	Basic bladder advice	Mean number of wet nights decreased after 3 months from 8.9 to 5.9 episodes every 2 weeks. BBA was fully successful in 2% o the children after 30 day, 12% after 60 days, and 18% after 90 days
Eliezer et al. (2021)	Clinical study	39 children with MNE and NMNE plus behavioural disorders	10.3 ± 2.0	27 boys 12 girls	Standard urotherapy Combination therapy with specific urotherapy or pharmacotherapy.	Following 3-month review, 14 (38%) children continued to receive standard urotherapy, while 15 (41%) children were transitioned to combination therapy. At 6-month review, complete/partial response was seen in 62% (23/37) and no response in 16% (6/37); with 32% (12/37) responding to standard urotherapy alone.
Borgström et al. (2022)	Randomized controlled trial	60 children with NE	7.2	44 boys 16 girls	Group A BBA Group B enuresis alarm Group C no treatment	The median number of wet nights out of 14 before and at the end of treatment were in group A (n = 20) 12.5 and 11.5, in group B (n = 22) 11.0 and 3.5 and in group C (n = 18) 12.5 and 12.0. The difference in reduction of enuresis frequency between the groups was highly significant (p = 0.002), but no difference was found between basic bladder advice and controls.
Cederblad et al. (2015)	Randomized controlled trial	40 children with NE	6 y	29 boys 11 girls	Group A BBA for 1 month and then alarm therapy Group B alarm therapy	No reduction of NE frequency in group A. 4 children in group A had a partial or full response to bladder training, and 2 of these children relapsed during alarm therapy.
Hascicek et al. (2019)	Randomized controlled trial	63 children with MNE	Group I 9.5 Group II 8.5 Group III 9	40 boys 23 girls	Group I behavioural therapy Group II behavioural therapy with a written checklist for parents Group III desmopressin treatment plus verbal behavioural therapy	High rates of treatment compliance in Gropu II. The treatment response rates in Group I were significantly lower compared to those of Group II and III with no statistical difference determined between Groups II and III

Table 2. *Continued*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Kajbafzadeh et al. (2015)	Randomized controlled trial	54 with primary NE	8.7 ±2.5	31 boys 23 girls	Control group standard urotherapy only Interferential (IF) electrical stimulation group standard urotherapy + IF electrical stimulation	15/27 (55.5%) and 6/27 (22%) of children in the IF and control groups responded to treatment at the 1-year follow-up. The mean number of wet nights per week in the control and IF groups decreased from 5.4 ±2 and 5.7 ±2 to 3.3 ±3 and 1.1 ±2, respectively, at first evaluation. The mean improvement score in the IF group was significantly higher than that of the control group after 1 year (78 vs 46%).
Mattsson et al. (2010)	Clinical study	200 children with bladder dysfunction and incontinence	7.2	84 boys 116 girls	Urotherapy in small groups (2–5), called voiding school (VS)	At follow up at 3 and 12 months, 35% and 40% were cured and another 30% and 34% improved. Compared with the year before start of VS, urinary tract infections decreased from 34% to 6%.
Ma et al. (2017)	Randomized controlled trial	369 children with NE	8.00 ±2.77	216 boys 153 girls	Suoquan Desmopressin plus suoquan, Desmopressin, or behavioral intervention	Complete response rate: 37.5% in the desmopressin plus suoquan group, 22.5% in the desmopressin group, 6.3% in the behavioral intervention group. Relapse rate 72.2% in the desmopressin group and 30.6% in the desmopressin plus suoquan group.
Ma et al. (2019)	Clinical study	666 children with NE	6.5	349 boys 317 girls	Normal weight group Overweight group Obesity group	The rates of severe enuresis in patients with normal weight, overweight, and obesity were 63.9%, 77.5%, and 78.6%, respectively. The complete response of the normal group was higher than those of the overweight and obese groups (26.8% vs. 14.0%, P = 0.010; 26.8% vs 0.0%, P = 0.000). Overweight children showed higher complete response than obese ones (14.0% vs 0.0%, P = 0.009).
Alsharnoubi et al. (2017)	Randomized controlled trial	45 children with NE	Group A 9.43 ±2.77 Group B 8.8 ±3.18 Group C 9.93 ±3.16	Not mentioned	Group A desmopressin acetate Group B laser acupuncture Group C laser acupuncture and desmopressin	Higher cure rate in group B (73.3 %) than in groups A (20%) and C (13.3%)

used long-term without substantial risks, and side effects are rare, with higher incidence of complications under intranasal desmopressin therapy [16]. The main side effect is the risk of water intoxication (vomiting, headache, decreased consciousness, possible seizures, and hyponatraemia) if this medication is combined with excessive fluid intake [16]. Anticholinergics are the second-line antienuretic therapy; there are several anticholinergic drugs available with effectiveness proven in several studies, such as trospium chloride, solifenacin, and tolterodine, but only oxybutynin (0.1–0.3 mg/kg/d) is available for label use in children [17]. Oxybutynin performs its action by decreasing detrusor overactivity, a crucial factor in the pathogenetic mechanism of NE, especially in NMNE or enuresis nonresponsive to desmopressin therapy. It is not typically effective as monotherapy, so it can be added to desmopressin in children who experience daytime incontinence owing to urgency, as well as in patients who do not respond to desmopressin alone [24, 25]. The medication is taken in the evening one hour before bedtime and should be started with a dose in the lower interval 2.5–5 mg [17]. The favorable effect, if any, may not be immediately apparent, so the therapy should be evaluated after 1–2 months [17]. The most clinically relevant side-effects in the paediatric population are constipation (which may in turn influence LUT function), post-void residual urine, and dry mouth (which may lead to caries) [26]. Before considering anticholinergic treatment, constipation and residual urine need to be excluded: if initial therapeutic response is good but

the wet nights start to reappear, constipation should be suspected, and residual urine should be monitored once after 3–6 months. The tricyclic antidepressant imipramine, approved by the US Food and Drug Administration for the treatment of NE, is an evidence-based antienuretic therapy (evidence level Ia) that can be used as a third-line alternative [27]. It works by decreasing REM time, stimulating antidiuretic hormone secretion, and relaxing the detrusor muscle [28]. Among therapy-resistant enuretic children, 30–50% may be expected to benefit from imipramine, and this proportion increases if desmopressin is added [29]. Imipramine should be given approximately one hour before bedtime. The dosage is 25–50 mg with a therapeutic response after one month [17]. It has various side effects (anxiety, dizziness, drowsiness, lethargy, dry mouth, anorexia, vomiting), the most common and limiting in clinical practice being mood swings and nausea, but the more serious one is cardiotoxicity, which has limited the use of tricyclics in enuresis [30]. In the case of overdose or a child affected by unstable arrhythmia (long QT-syndrome), a fatal reaction may occur [31]. Thus, the drug should not be given without prior long-time electrocardiographic evaluation in case of positive anamnesis (history of unclear syncope/palpitations in the child, positive family history of sudden cardiac death). Few studies have studied the use of imipramine, usually in association with desmopressin. Ravanshad et al. investigated the efficacy of low-dose imipramine combined with desmopressin on the treatment of patients defined as desmopressin non-responders. Their analysis showed that low-dose imipramine is well tolerated in clinical practice and may represent a good short-term treatment option in combination therapy where desmopressin alone was not sufficient [32]. The noradrenergic drug mirabegron has recently proven to be an efficient and safe addition or alternative to anticholinergics in adults with detrusor overactivity, and future research could determine its possible role in children with enuresis [33]. An observation study by Kim et al. compared the efficacy and tolerability of mirabegron and solifenacin in paediatric patients with idiopathic overactive bladder. They reported a comparable efficacy of mirabegron to solifenacin in paediatric patients with drug-induced adverse effects in only 10% of the solifenacin-treated patients [34]. Moreover, in a recent multicentre study conducted in paediatric patients with neurogenic detrusor overactivity, mirabegron increased bladder compliance, bladder volume until first detrusor contraction, the average volume per catheterization, the maximum daytime catheterized volume, and the number of dry days per week, with a significant improvement in quality of life and symptoms. Mirabegron seemed to be effective and well-tolerated in the treatment of paediatric patients with neurogenic detrusor overactivity, and it received its first approval in this indication in paediatric patients aged ≥ 3 years [35]. The combination therapy has been used in many clinical trials, especially in children resistant to desmopressin monotherapy, underlying the possibility of a major response and effectiveness in the case of multiple drugs. Esteghamati et al. conducted a randomized controlled trial to compare the efficacy of desmopressin plus tolterodine with desmopressin plus indomethacin in NE resistant to desmopressin monotherapy. They found that desmopressin plus tolterodine was superior, with complete response to treatment and lower treatment failure [36]. According to this, Kamperis et al. investigated the effect of combining indomethacin and desmopressin or desmopressin and placebo. Although the combination of indomethacin and desmopressin significantly reduced nocturnal urine output, it seemed to be ineffective in increasing dry nights in all children and in reducing enuresis frequency [37]. A trial conducted in 2021 in 62 patients with primary NE compared the therapeutic efficacy of the following treatments: solifenacin plus desmopressin, tolterodine plus desmopressin, and desmopressin alone. Although desmopressin has been used as a first drug, this study documented a higher response in combination therapy groups of desmopressin plus anticholinergic than the monotherapy group [38]. Austin et al. compared in a randomized controlled trial the use of combination therapy with desmopressin and an anticholinergic medication for non-responders to desmopressin. After one month of treatment, there was a significant reduction in the mean number of wet nights, with a significant 66% decrease in the risk of a wet episode, compared with the placebo group [39]. The implementation of anticholinergic agents may play an important role for a subset of children with enuresis who have a restricted bladder capacity and thickened bladder wall, as demonstrated by Montaldo et al., who assessed the efficacy of desmopressin plus oxybutynin in a randomized, double-blinded, placebo-controlled trial for 206 children with monosymptomatic NE (MNE) resistant to desmopressin [14). Lee et al. confirmed this data by evaluating the efficacy of a combination of desmopressin and oxybutynin compared to the single drugs imipramine and desmopressin for treating children with NE. Combination therapy produced the best and most rapid results regardless of whether the children had monosymptomatic or polysymptomatic enuresis. Combination therapy with desmopressin plus oxybutynin for the treatment of paediatric NE was well

tolerated and gave significantly faster and more cost-effective results than single-drug therapy using either desmopressin or imipramine [40].

Non-pharmacological therapy

Enuresis alarm

Few treatments are empirically established for NE, and they are typically divided into pharmacological and non-pharmacological approaches [41]. Despite the pharmacological options, alarm treatment is still one of the main approaches used nowadays, with no side effects, a great rate of response and a success rate between 50% and 70% [42]. A clinical trial, conducted by Van Leerdam et al., reported a high success rate both in MNE and NMNE with a clinical improvement also 2 years after alarm treatment [43]. The full response in the long-term was described by Ozgür et al., who documented complete dryness in 32% (13/40) of patients at the end of a one-year period, although a relapse was observed in 66.7% [44]. Alarm treatment consists of a device that provides an arousal stimulus to the child and family when urine activates a detector placed in the child's bed or clothing [45]. Four forms of night alarms have been studied: sound, vibration, one that mixes an electrical impulse and a sound, and code words [46]. The use of acoustic stimuli, the most used, is configured in many ways with the same efficacy; it is associated with light or not, awakening the child immediately or after 3 minutes, putting a moisture sensor within the child's underclothing or just on the bed, alarming the parents or the child only [46]. The main aim of an enuresis alarm is to advise and educate the child to respond quickly and appropriately to a full bladder during sleep, transforming the signal from one of urination to that of inhibition of urination and waking [41]. Thus, the goal of an enuresis alarm is to train children to wake up for micturition before incontinence or to prevent emptying the bladder while asleep [47]. The mechanism of action of enuresis alarm systems is not fully understood, even if it is believed to involve amelioration of arousal in response to a full bladder. Taneli et al. in 2004 conducted a clinical trial on 28 children with MNE, evaluating the functional bladder capacity before and after a treatment period of 12 weeks. They documented a significant increase in bladder storage capacities (maximum nocturnal bladder capacity, maximum functional bladder capacity, and mean day-time bladder capacity) underlying that the effectiveness of alarm treatment is due not only to classical conditioning but it is also probably related to increases in bladder storage capacities [48]. Other possible mechanisms have been studied by Butler et al., who hypothesized that, in a small sample of patients, dryness was achieved through a rise in osmolality in association with arginine vasopressin (AVP) release in children with NE and nocturnal polyuria (possibly lacking AVP release) and a rise in osmolality, with no change in AVP levels, in children with small bladder volumes (possibly overactive and with more concentrated urine) [49]. The most effective period of alarm treatment is about 16–20 weeks of continuous therapy, even if sometimes 2–3 months are considered enough for being dry for 14 consecutive days [46]. A randomized controlled trial, conducted by Kirill V Kosilov et al., compared the efficacy of alarm intervention after 12 weeks, 16 weeks, and 20 weeks. They documented the maximum effectiveness of treatment and the stability of long-term results after the range of time 16–20 weeks, maybe due to the formation of a neuroreflexive mechanism that created a habit for independent awakening in children with MNE [50]. Alarm therapy is considered the first treatment modality of choice for enuresis with a better treatment response, also in cases of relapse, and a lower recurrence rate as compared to other modalities of treatment [46, 47]. A meta-analysis by Pan Song et al. compared multiple treatments (desmopressin, alarm, desmopressin plus alarm, and desmopressin plus anticholinergic agent) in the management of MNE focusing on complete response and success rates. Although desmopressin plus an anticholinergic agent had higher success rates than desmopressin or alarm monotherapy, alarm therapy had the lowest relapse rate [51]. Naitoh et al. conducted a clinical trial in which they documented that the combination therapy with alarm and drugs for MNE was not superior to alarm monotherapy, considering multiple therapy as a second choice in the case of non-response [52]. The relapse rate was assigned to family situation, behaviour deviance in the child, and the educational level of the parents. The variable length of enuresis alarm was associated with a dropout rate of 10–30% [45]. A motivated child and compliance of the family, who must be totally informed in a comprehensive manner, is a critical favourable prognostic indicator for alarm therapy, as declared by the International Children's Continence Society [43]. It is demonstrated by a wide range of trials such as the study by Tsuji et al. that demonstrated a similar efficacy both in children awakened by family members and in children self-responsible for waking to the alarm [53]. Sleep deprivation and behavioural problems, such as attention deficit hyperactivity disorder (ADHD), are prognostic factors to be considered [43].

Dietary Intervention

Diet changes, including reduced fluid intake before bedtime, reduced consumption of foods and drinks containing caffeine, reduced consumption of carbonate drinks, are usually recommended in recent years, because it has been established that some foods and beverages can promote diuresis or detrusor over-activity [54, 55, 56]. For example, restricted fluid intake after 6 p.m. (or 3–4 h before bedtime) may reduce the total overnight urine production and thus the child's need to void overnight. Carbonated drinks and artificial sweeteners may contribute to overactive bladder symptoms while caffeine also has a diuretic effect [57]. Ferrara et al. listed recommended and non-recommended foods in children with NE [57]:

- Recommended foods: vegetables, fish, seafood, dried fruits, cereals, and eggs
- Non-recommended foods: salt, chocolate, cocoa, carbonated drinks, tea, and fruit juice
- Non-recommended foods in the evening: fruit, water, yogurt, cheese, and milk.

Dietary recommendations are based on pharmacological and clinical studies underlying possible mechanisms of NE pathophysiology. Nikibakhsh et al. considered hypercalciuria an important pathogenic factor of NE because it seems to decrease the amount of aquaporin-2 detectable in the urine, and urinary excretion of AQP2 in humans has been proposed as a potential marker of collecting-duct responsiveness to vasopressin. Moreover, hypercalciuria seems to be correlated with desmopressin resistance [58]. Thus, Ferrara et al. did not recommended ripened cheese, such as parmesan cheese, grana Padano, and pecorino (Italian sheep cheese) at every meal because aged cheeses were too rich in calcium, and they recommended vegetables rich in oxalate and phytate that inhibit bowel calcium absorption [57]. Evidence of lower levels of vitamin B12 and folate in enuretic chil¬dren, maybe involved in neurogenic maturation and nocturnal bladder control, led to the suggestion of eating foods rich in them such as meat, fish, albumen and yolk, seafood, wheat germ, wheat bran, corn flakes, crisped rice, asparagus, and turnip greens [57, 59]. However, clinical trials and a larger sample of enuretic children are needed to establish the effectiveness of diet advice.

Pelvic floor retraining

Pelvic floor rehabilitation is a behavioural and exercise-based treatment approach to NE, firstly introduced as a specific urotherapy by Wennergren and Oberg to increase children's awareness of their pelvic floor muscles and its contraction and relaxation [60]. The use of pelvic floor retraining is based on the hypothesis that NE, but also daytime incontinence, in children may be due to muscle overactivity and ligament weakness that destabilize control of the micturition reflex [61]. Despite the larger implementation in NE management, no exercise protocol has been standardized, with variations in the number of repetitions, duration of contraction and relaxation, and period of training. A trial conducted by Campos et al., including children with NE and other lower urinary tract symptoms, compared standard urotherapy alone with pelvic floor muscle training alone and in combination with oxybutynin. Standard urotherapy consisted of behavioural modification, proper voiding posture, bowel habits, and voiding intervals at every 2 hours, while pelvic floor exercises were 2 series of 10 maximal effort pelvic floor muscle contractions, totalling 20 contractions per session with a electromyography biofeedback. They showed no difference in treatment results, also after 2 years, documenting that all treatment modalities were effective regarding improved enuresis and lower urinary tract symptoms [62]. Vesna et al. reported after one year of therapy a significantly larger number of cured children, who suffered from urinary incontinence and NE, if subjected to diaphragmatic breathing and pelvic floor muscles, while Van Kampen et al. established no beneficial effect of including pelvic floor muscle training in full-spectrum therapy [59, 63, 64]. Squatting and diaphragmatic breathing exercises are the main protocols used. Squatting-based pelvic floor exercises are based on the results of Petros et al. in a premenopausal adult population, in whom they strengthened involuntary pelvic muscles and the ligaments they contracted against, with improvement of nocturia, stress urinary incontinence and bowel symptoms in 70–90% of premenopausal women [65]. Garcia-Fernandez et al. evaluated the role of squatting exercises, compared with a control group in which children ran 50 metres in the morning and at night, in children with NE after 4 weeks and 4 months of treatment. Squatting exercises included 10 squats morning and evening at home, 10 bridge exercises morning and evening at home, and fitball exercises involving pelvic anteversion and retroversion once a week, which involved proprioception exercises with surface perineal electromyography. At 4 weeks 12/24 in the treatment group reported total cure of wetting while 41/48 children (86%) were cured of both daytime/nighttime enuresis at 4 months [66].

Diaphragmatic breathing is an exercising technique to help strengthen the diaphragm. In a lying or sitting position, children are asked to inhale the air through the nose, bulge the abdomen outwards as

much as possible, hold their breath for a few seconds, and then exhale slowly through pursed lips.
Children are asked to watch the anterior abdominal wall movement during inspiration and repeat the same action when they start voiding. Zivkovic et al. conducted research in children with dysfunctional voiding to investigate the function of abdominal and pelvic floor training. After one year of therapy, most children did not present urinary incontinence, NE, and urinary tract infections: urinary incontinence was cured in 20 out of 24 patients (83%), and NE in 12 out of 19 children (63%) [66]. Despite the controversial results, pelvic floor rehabilitation remains an effective, inexpensive, and simple tool to integrate into the management of NE [67].

Bladder training

According to the International Children's Continence Society, standard therapy or basic bladder advice (BBA) includes a wide range of interventions such as education, lifestyle changes, registration of symptoms, and support for the child and the family to optimize voiding patterns and improve bladder dysfunction such as enuresis [68, 69]. Although fewer trials have studied BBA in enuretic children, with strong evidence especially in children with day-time voiding problems, it is recommended as first-line therapy against enuresis regardless of the underlying condition [70].
Recent clinical trials have shown limited efficacy of BBA, mostly pronounced after the third month of therapy, while other studies supported its effectiveness and good response, with about a third of children responding to standard therapy alone [68, 70, 71]. Moreover, the duration of BBA as monotherapy and its efficacy in MNE is still a matter of debate. The duration of BBA in the study by Cederblad et al. was one month, with a complete response in 5% of children, while in the study of Kajbafzadeh et al. and Hascicek et al., with 2 months of therapy, the response rates were 25% and 30%, respectively [72, 73, 74]. Thus, a longer time window is recommended for a higher rate of response. The intensity of the intervention regimen might affect the response. Hascicek et al. documented that the implementation of a written checklist of behavioural instructions improved therapy and its effectiveness, while Mattsson et al. enrolled 200 children with bladder dysfunction and incontinence to participate in voiding schools in small groups, a multidisciplinary combined in- and outpatient bladder rehabilitation program, with higher response rate [74, 75]. Efficacy of urotherapy might be influenced by predictive factors such as gender, age (higher compliance and response in older children), maternal education level, frequency of symptoms, overweight, and obesity [76, 77]. Despite the conflicting available data, low cost, and lack of risk make urotherapy a first-line treatment in NE, it might more efficient as an add-on to other first-line treatments instead of an independent intervention.

Acupuncture

Acupuncture has been used as a primary therapy for NE, especially in Asia, with evidence from clinical trials and systematic reviews of positive effects, despite a great heterogeneity, suggesting that some forms of acupuncture might be more effective than others, and disparate results from similar interventions [78]. Acupuncture is based on the theory of 12 primary meridians or energy channels along which are distributed 360 acupuncture points. The sites used to treat bladder dysfunction coincide with innervation by spinal sacral segments S2 through S4, and the stimulation of these acupoints (manual pressure, penetration of the skin, heating, the application of laser, electrotherapy, or moxibustion) should cause homeostatic changes [78]. A comparative study conducted by Alsharnoubi et al. evaluated the effect of using laser acupuncture and medication for the treatment of children with NE. They documented a significantly higher cure rate of about 73.3%, in children subjected to laser acupuncture, while response to traditional therapy was about 20% [79]. However, although acupuncture is a noninvasive painless tool, it is not suggested by clinicians and not recommended in guidelines.

Complementary interventions

Other treatments have been considered in NE, but they are not recommended because they have insufficient data to recommend their use in children with NE, based mostly on the poor quality of the data available for analysis. A Cochrane review conducted in 2005 investigated psychotherapy and counselling, suggesting their use in the management of children with psychological problems in addition to enuresis. On the other hand, hypnosis and homeopathy are not included in the recent guidelines and are considered as less traditional approaches used to treat bedwetting [80]. These alternative therapies need more data from quality randomized trials, but they may be incorporated in a more complex treatment plan for refractory children.
In severely therapy-resistant enuresis, the endoscopic injection of botulinum toxin and sacral neurostimulation have been studied as alternative treatments,

even if they are not recommended as first- and second-line treatments because of the lack of evidence and randomized clinical trials. A pilot study by Jung et al. including 27 patients with NME, who showed no response after conservative treatment for more than 12 months, documented an improvement of detrusor overactivity after intravesical botulinum toxin injection up to one year later, while Hoebeke et al. reported positive long-term results in 70% of children after a single injection [81, 82]. There are limited data on the effectiveness of sacral nerve stimulation in children. A clinical trial by Humphreys et al. studied the effectiveness of sacral nerve stimulation in children affected by urinary symptoms (dysfunctional voiding, enuresis, incontinence, urinary tract infections, bladder pain, urinary retention, urgency, frequency) and bowel symptoms. The study documented an improvement of urinary incontinence in 84%, improvement of enuresis in 69%, and improvement of urinary retention in 60% [83]. Sacral neuromodulation via implanted pulse generator, as a treatment for children with dysfunctional elimination syndrome and symptoms refractory to maximum medical therapy, has been studied in the 10-year single-centre experience by McCrery et al., showing an improvement of urinary incontinence, constipation, frequency and/or urgency, and enuresis [84]. However, larger samples and randomized clinical trials are required to understand and assess the use of botulinum toxin injection and nerve stimulation in enuresis treatment.
Moreover, a multidisciplinary approach is recommended because comorbidities are one of the main factors to be considered in the global management of NE, as demonstrated by clinical studies in which their improvement reduced NE severity and improved treatment response [85–88]. For example, Juszczak et al. reported obstruction of the upper airway tracts, causing sleep apnoea and other breathing abnormalities, as a predictive factor in NE, as well as the positive effect of maxillary expansion on reducing bedwetting symptoms [89]. This evidence was based on previous studies, such as one by Oshagh et al., who documented in a preliminary study the reduction of the frequency of wetting during the period of appliance of slow maxillary insertion without expansion. During the expansion and retention phase, 2 patients became completely dry, and 2 patients improved significantly [90]. Sleep dysregulation and constipation are the other 2 main comorbidities affecting NE. Several studies have already shown that a wide range of comorbidities influence the prognosis and the response to the therapy in enuretic children [85–94].

CONCLUSIONS

NE is a common health problem. Different medical disciplines deal with children with enuresis and their families: paediatrics, paediatric nephrology, and paediatric urology, in addition to child psychology and child psychiatry, urotherapists, and others. Multiple treatment approaches, both pharmacological and non-pharmacological, have been established and validated by the ICCS to reduce signs and symptoms of NE and improve quality of life and the social and emotional discomfort experienced by children. The aim of paediatricians is to identify the right therapy protocol for very single child, evaluating the best approach for the child and their family. Overall, all the pharmacological and non-pharmacological approaches to NE appear to be useful, with the latest innovative approaches looking promising even if further randomized clinical trials including a wide range of patients are necessary to validate these methods and develop standardized protocols shared in the scientific community.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

FUNCTIONAL UROLOGY

Detrusor underactivity and complicated stress urinary incontinence: a cross-data study

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Introduction It is still uncertain whether detrusor underactivity (DUA) influences the outcomes of women undergoing surgery for stress urinary incontinence (SUI). Even less evidence is available about women with complicated stress urinary incontinence (C-SUI). The aim of the study was to assess outcomes of middle urethral sling (MUS) placement according to the type of SUI, and the impact of DUA on uncomplicated SUI (U-SUI) and C-SUI functional and surgical results.

Material and methods The study was conducted among patients undergoing MUS. The population was divided into 4 groups: 1: C-SUI with DUA; 2: C-SUI without DUA; 3: U-SUI with DUA; and 4: U-SUI without DUA. Women were qualified for the DUA group if they met one of the Jeong, Abarbanel and Marcus, BVE, and PIP1 Griffiths criteria. Post-operative functional outcomes and differences in POUR rate, de novo overactive bladder syndrome (OAB), and SUI recurrence were examined.

Results 142 women took part in the study, of whom 97 completed the 2-year follow-up. DUA was found in 54.6% (53/97) of patients. C-SUI was prevalent also in the no-DUA group (59.1%). Post-operative ICIQ-FLUTS improved more in the no-DUA patients compared to the DUA women. Post-operative Qmax was statistically significant higher the in no-DUA than in the DUA population. After surgery, neither the PVR nor the PVR ratio differed in the DUA and the no-DUA patients. C-SUI and U-SUI patients showed a POUR rate of 15.6%–12.1%, de novo OAB 12.5%–3%, tape incision 3.1%–3%, and SUI recurrence 4.6%–3%, respectively.

Conclusions The impact of pre-operative DUA on the outcomes of patients undergoing MUS was negligible, even in C-SUI cases. DUA women with SUI, even if complicated, should not be excluded from this kind of surgery.

Key Words: urodynamics ‹› detrusor underactivity ‹› complicated stress urinary incontinence ‹› uncomplicated stress urinary incontinence ‹› middle urethral sling

INTRODUCTION

Stress urinary incontinence (SUI) is the complaint of involuntary loss of urine with physical exertion or other activities that cause a rise in intra-abdominal pressure [1]. The incidence of SUI is estimated at 3%, with the main risk factors being age, ethnicity, and body mass index (BMI) [2]. Other factors related to SUI are parity and previous hysterectomy or pelvic surgery.

SUI can be divided into uncomplicated (U-SUI) and complicated (C-SUI), which is generally related to lower urinary tract dysfunction. Complicated SUI is a clinical diagnosis involving the association with disorders, comorbidities, and previous surgery or radiotherapy of the pelvic area or the lower urinary tract. Also, patients not naïve for SUI surgery are considered as C-SUI. Women reporting only SUI and with no associated disorders of the pelvic area and lower urinary tract a history are defined as U-SUI. However, C-SUI can be defined in multiple ways; the American Urological Association guidelines, for example, discern index patients, otherwise

healthy females who are candidate for surgery for SUI, from non-index patients, in whom SUI is associated with other lower urinary symptoms, pelvic organ prolapse, or previous pelvic surgery [3]. According to the International Continence Society (ICS), women affected by C-SUI are those who underwent previous surgery for incontinence, prior extensive pelvic surgery, or pelvic irradiation, have suspected urinary fistula or suffer from pain, haematuria, recurrent infection, or statistically significant voiding symptoms. Patients who do not fall into these categories are labelled as affected by U-SUI [1]. Currently, the most frequent surgical procedure for female SUI is mid-urethral sling (MUS) where available [4]. The MUS subjective cure rate has been reported up to 98%, depending on the definition of success, the modality of follow-up (telephone follow-up, objective or subjective success rate, follow-up duration), the route of insertion, and the cohort under study [5, 6, 7]. Even though slightly worse outcomes have been observed among the C-SUI population [8], MUS positioning is recommended for either type of SUI.

Preoperative invasive urodynamics (UD) is not routinely recommended in U-SUI patients, after several RCTs showed its irrelevance in terms of surgical outcomes in this population [3, 4, 9–12]. On the contrary, there is still general consensus on routinely performing UD in C-SUI patients.

Detrusor underactivity (DUA) is defined by the ICS as detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span [1]. The definition relies on UD, even though it lacks standardized parameters. Moreover, the broad range of symptoms that can be observed in this condition makes it difficult to delineate a pathognomonic clinical sign of DUA. Underactive bladder syndrome (UAB) was recently referred to as a clinical syndrome correlated with DUA [13]. This definition is accepted by the ICS, even though it is insufficient to confidently recognize detrusor underactivity from a clinical point of view. Thus, the diagnosis remains challenging, and its true incidence still uncertain. To overcome this issue different urodynamic criteria have been proposed. The most used are those by Jeong et al. [14], Abarbanel and Marcus [15], the BVE criteria [16], and Griffiths-PIP1 [17]. These criteria rely on different thresholds and are thus unsuitable for a homogeneous and unique definition of DUA.

To date, it is uncertain whether DUA influences the outcomes of women undergoing surgery for SUI, given the lack of published data [18, 19]. Even less evidence is available of what concerns women affected by C-SUI.

C-SUI and DUA are recognized as potential conditions affecting MUS results; however, available studies have assessed these factors only separately, not analysing the relationship between C-SUI and DUA and the potential impact of DUA on the results of the type of SUI [18, 19, 20]. Our research aimed to clarify the influence of each of these conditions – the type of SUI and detrusor impairment – on MUS positioning. Therefore, the purpose of this study was to assess outcomes of MUS placement according to the type of SUI (U-SUI versus C-SUI) and the impact of DUA on U-SUI and C-SUI functional and surgical results.

MATERIAL AND METHODS

This was a prospective study including women who underwent surgery for SUI from January 2015 to January 2019 at a tertiary high-volume referral centre. Female patients aged 18 years or older diagnosed with SUI, who chose to undergo trans-obturator MUS (in-out) implantation, naïve or not for SUI surgery, with or without pelvic organ prolapse were included. Exclusion criteria were inability to sign informed consent, fixed urethra and neurogenic bladder as spinal cord injury, multiple sclerosis, Parkinson's disease and major central and spinal cord neurogenic disorders, and missing objective evaluation at follow-up. After adequate counselling, patients were offered the MUS procedure as the first-choice treatment. Informed consent for the surgical procedure and for participation in the study was collected from each patient. All surgical procedures were performed by 2 skilled surgeons (M.B. and E.R.).

Pre-operative evaluation included medical history, physical examination, and UD according to Good Urodynamic Practice [21]. Furthermore, the ICIQ-FLUTS questionnaire was administered to each patient [22]. Women were affected by DUA if they belonged to at least one of the categories defined by Jeong [14], Abarbanel and Marcus [15], BVE [16], and PIP1 Griffiths criteria [17].

Afterward, the population was divided into 4 groups depending on the presence of DUA and the kind of SUI: 1: C-SUI with DUA; 2: C-SUI without DUA; 3: U-SUI with DUA; and 4: U-SUI without DUA. The bladder catheter was removed 24 hours after surgery and three consecutive bladder scan testing were performed before discharge. Due to the lack of accepted standardized definition of post-operative urinary retention (POUR), we considered it as the occurrence of PVR ≥200 ml in ≥2 evaluations. This definition is among the most accepted and reported in the literature [23, 24]. Treatment options for POUR were clean intermittent catheterization

(CIC) or indwelling catheter (IC) depending on the patient's choice. In the case of persistent POUR (>30 days), tape incision or persistent catheterization were proposed after adequate counselling. Success of the intervention was defined as negative stress tests at 250–300 ml repletion in supine and standing position by coughing and Valsalva manoeuvres.

Follow-ups were scheduled at 3, 6, and 12 months and then annually, by office evaluation including physical examination, UF, ICIQ-FLUTS, PVR, and PVR ratio. All patients reached at least 2 years of follow-up. Post-operative functional outcomes and the differences between the 2 SUI populations were investigated. We also evaluated differences in the following: POUR rate, de novo overactive bladder syndrome (OAB), and SUI recurrence.

Student's T-test for continuous parametric variables and Pearson's chi-squared test for independent variables were used for statistical analysis.

Ethical standards were performed according to the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained before enrolment in the study. The Local Ethics Committee for Clinical Trials (CESC) determined that approval for this investigation was unnecessary because it only involved standard clinical practice. This research was registered in the clinical audit in our hospital.

RESULTS

A total of 193 women underwent MUS positioning, of whom 142 were eligible for this study and 97 completed the 2-year follow-up. The C-SUI group comprised 64 patients (66%), while the remaining 33 (34%) women showed a U-SUI. DUA was found in 54.6% (53/97) of patients; most of them (71.7%) suffered from C-SUI. C-SUI was the prevalent form of incontinence in patients without DUA (59.1%), as well (table 1). Table 2 reports pre-operative and post-operative data for females with C-SUI, while table 3 shows data for U-SUI. The mean age was 63.6 ±9.6 for patients with DUA and 59.5 ±11.1 for patients without DUA.

C-SUI and U-SUI groups showed de novo OAB 12.5% and 3%, tape incision 3.1% and 3%, and SUI recurrence 4.6% and 3%, respectively. No statistically significant difference was observed between the above data between the C-SUI and U-SUI groups.

Women with C-SUI showed a mean pre-operative ICIQ-FLUTS of 84.9 ±24.2 in DUA patients, and 79 ±24.7 in the no-DUA population (p = 0.3). Conversely, U-SUI patients reported an ICIQ-FLUTS of 77.5 ± 27.9 and 78 ± 23.8 for the DUA and no-DUA groups, respectively (p = 0.9). Mean pre-operative Qmax was statistically significantly higher among the no-DUA population compared to the DUA population, either if affected by complicated or uncomplicated SUI. The pre-operative PVR and PVR ratio did not statistically significant differ in both sub-groups of SUI.

Post-operative ICIQ-FLUTS improved more in the no-DUA patients than in the DUA women, but without statistical significance. Furthermore, post-operative urinary symptoms, assessed with ICIQ-FLUTS scores, did not statistically significantly differ according to SUI type. Post-operative Qmax was statistically significantly higher in the no-DUA than in the DUA population. After surgery, neither PVR nor PVR ratio differed statistically significantly in the DUA and no-DUA populations, in both study arms. Moreover, there was no statistically significant difference in terms of bladder emptying features (Qmax and PVR) between the C-SUI and U-SUI groups.

The POUR rate was slightly higher in the C-SUI group (15.6%), in which we observed 10/64 cases. Six of these episodes happened in patients with DUA. However, in women with U-SUI we registered a mean POUR rate of 12.1%, and all of them had pre-operative DUA. Nevertheless, there was

Table 1. *Data stratified according to type of stress urinary incontinence and detrusor contractility*

	C-SUI, n = 64 (66%)		U-SUI, n = 33 (34%)	
	DUA	No DUA	DUA	No DUA
N, %	38 (59.4%)	26 (40.6%)	15 (45.9%)	18 (54.5%)
Age (mean, SD)	63.6 (±9.4)	61 (±10.7)	63.8 (±9.9)	60 (±11.3)
	DUA, n = 53 (54.6%)		No DUA, n = 44 (45.4%)	
	C-SUI	U-SUI	C-SUI	U-SUI
N, %	38 (71.7%)	15 (28.3%)	26 (59.1%)	18 (40.9%)
Age (mean, SD)	63.6 (±9.4)	63.8 (±9.9)	61 (±10.7)	60 (±11.3)

C-SUI – complicated stress urinary incontinence; U-SUI – uncomplicated stress urinary incontinence; DUA – detrusor underactivity; No DUA – no detrusor underactivity; SD – standard deviation.

Table 2. *Functional and surgical data of complicated stress urinary incontinence patients with and without detrusor underactivity*

	Pre-operative			Post-operative		
	DUA	NO DUA	p-value	DUA	NO DUA	p-value
ICIQ-FLUTS	84.9 ±24.2 84.9 ±24.2	79 ±24.7 79 ±24.7	0.3	26.3 ±25.4 26.3 ±25.4	16 ±24.3 16 ±24.3	0.1 <0.05 <0.05
Q Max	12.2 ±4.9 12.2 ±4.9	21.1 ±8.2 21.1 ±8.2	<0.05	16.7 ±4.7 16.7 ±4.7	23.4 ±5.9 23.4 ±5.9	<0.05 <0.05 0.2
PVR	92.3 ±134.2 92.3 ±134.2	56.9 ±119.9 56.9 ±119.9	0.2	27.1 ±55.9 27.1 ±55.9	30.9 ±47.5 30.9 ±47.5	0.7 <0.05 0.2
PVR ratio	0.08 ±0.1 0.08 ±0.1	0.09 ±0.1 0.09 ±0.1	0.7	0.08 ±0.1 0.08 ±0.1	0.09 ±0.1 0.09 ±0.1	0.7 1 0.4
POUR				6/38 (15.8%)	4/26 (15.4%)	0.7
CIC duration (days)				3/38 (7.9%) 8.8 ±49.3	1/26 (3.8%) 0.2 ±1.4	0.9 0.3
Indwelling catheter duration (days)				4/38 (10.5%) 0.8 ±2.3	4/26 (15.4%) 2.1 ±6.3	0.9 0.2
Tape incision				1/38 (2.6%)	1/26 (3.8%)	0.6
De novo OAB				4/38 (10.5%)	4/26 (15.4%)	0.9
Recurrence SUI				2/38 (5.2%)	1/26 (3.8%)	0.7

DUA – detrusor underactivity; No DUA – no detrusor underactivity; PVR – post-void residual; POUR – postoperative urinary retention; CIC – clean intermittent catheterization; OAB – overactive bladder syndrome, SUI – stress urinary incontinence.

Table 3. *Functional and surgical data of uncomplicated stress urinary incontinence patients with and without detrusor underactivity*

	Preoperative			Postoperative		
	DUA	NO DUA	p-value	DUA	NO DUA	p-value
ICIQ-FLUTS	77.5 ±27.9 77.5 ±27.9	78 ±23.8 78 ±23.8	0.9	20.2 ±14.8 20.2 ±14.8	11.4 ±26.8 11.4 ±26.8	0.2 <0.05 <0.05
Q Max	12.7 ±4.6 12.7 ±4.6	22.4 ±5.3 22.4 ±5.3	<0.05	14.4 ±7.2 14.4 ±7.2	21.1 ±6.3 21.1 ±6.3	<0.05 0.4 0.5
PVR	18.6 ±38.9 18.6 ±38.9	13.3 ±29.5 13.3 ±29.5	0.6	24.1 ±39.2 24.1 ±39.2	23.8 ±32.5 23.8 ±32.5	0.9 0.7 0.3
PVR ratio	0.07 ±0.1 0.07 ±0.1	0.04 ±0.1 0.04 ±0.1	0.4	0.03 ±0.8 0.03 ±0.8	0.09 ±0.1 0.09 ±0.1	0.07 0.2 0.1
POUR				4/15 (26.6%)	0/18 (0%)	0.1
CIC duration (days)				2/15 (13.3%) 4 ±10.5	0/18 (0%)	0.4 0.1
Indwelling catheter duration (days)				2/15 (13.3%) 0.8 ±2.6	0/18 (0%)	0.4 0.2
Tape incision				0/15 (0%)	1/18 (5.5%)	0.9
de novo OAB				0/15 (0%)	1/18 (5.5%)	0.9
Recurrence SUI				0/15 (0%)	1/18 (5.5%)	0.9

DUA – detrusor underactivity; No DUA – no detrusor underactivity; PVR – post-void residual; POUR – postoperative urinary retention; CIC – clean intermittent catheterization; OAB – overactive bladder syndrome, SUI – stress urinary incontinence

no statistically significant difference among POUR rate, POUR treatment (CIC or indwelling catheter), and duration of bladder drainage between the DUA and no-DUA groups despite the sub-group of SUI.
We observed a mean tape incision rate of 3.1% and 3% in C-SUI and U-SUI patients, respectively.
Regarding de novo OAB and SUI recurrence, we did not find differences in the C-SUI and U-SUI groups despite detrusor contractility status, with a de novo OAB rate of 12.5% and 3% and a SUI recurrence rate of 4.6 and 3%, respectively.

DISCUSSION

Overall, the C-SUI group did not have inferior results to the U-SUI group, showing that the type of SUI based on clinical features had no relevant influence on surgical complications and success rates.
Post-operative voiding complications, POUR, and bladder emptying function did not statistically significantly differ, according to clinical and urodinamically demonstrated C-SUI or U-SUI. The success rate was high in both groups. However, the observation of a 4-fold higher rate of de novo OAB in C-SUI highlights the importance of adequate counselling in this subgroup of patients about this potential complication.
To our knowledge, this is the first study to cross-reference data on detrusor contractility, SUI, and outcomes after SUI surgery. DUA did not influence results and patients' satisfaction after MUS implantation. Interestingly, in the C-SUI group the DUA and no-DUA patients experienced almost the same number of post-operative voiding complications. Conversely, in the U-SUI group, the POUR rate was 4 times higher in patients with DUA. A possible explication was that in the 'U-SUI and DUA' subgroup, detrusor impairment was the only pathological condition of the lower urinary tract and pelvic area, while C-SUI can be associated with multiple other conditions affecting the lower urinary tract. Therefore, it is likely that detrusor impairment was more impactful on POUR in the 'U-SUI and DUA' subgroup than in the 'C-SUI and DUA' subgroup.
Based on these findings, DUA should neither be a contraindication nor a limitation to SUI surgery, regardless of SUI type, and C-SUI patients with DUA should also be considered good candidates for this treatment. Due to the lack of previous reports on the occurrence of complicated or uncomplicated SUI and the relationship between DUA and the kind of SUI, our new data are relevant to the scientific community. Different studies showed that DUA could be related to a prolonged return to normal voiding and higher post-operative urinary complications [19, 25]. Others found that preoperative Pdet/Qmax [18] or Qmax [20] could be predictive factors of a negative effect of DUA on SUI surgical outcomes. However, the lack of correlation between DUA and the type of SUI did not allow an assessment of whether DUA or C-SUI affected the voiding complications. Our data highlight that, regardless the category of SUI, the MUS outcomes were successful. DUA can exert its negative influence on the POUR rate, mostly in U-SUI women rather than in C-SUI. Thus, our study showed that neither the type of SUI, nor the detrusor impairment can be identified as negative predictive factors for surgical outcomes of MUS.
A limitation of our study was that all patients underwent transobturator MUS. Thus, we did not investigate the effect of retropubic route MUS on complicated and uncomplicated SUI. Another limitation is the sample size, which did not allow for a high number of events, such as POUR. The observed trend of a higher number of POUR episodes in patients with DUA could have been confirmed with a higher number of patients. This limitation did not affect the validity of our finding because each episode was transient.

CONCLUSIONS

Our data showed that the impact of pre-operative DUA on outcomes of patients undergoing MUS was negligible, even in C-SUI cases. DUA women with SUI, even if complicated, should not be excluded from this surgical treatment.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL STANDARDS

Ethical standards were performed according to the 1964 Declaration of Helsinki and its later amendments.
Local institutional review board and ethics committee (A.O.U.I Verona, dept. of Urology, University of Verona) approvals were obtained.
The Local Ethics Committee for Clinical Trials (CESC) determined that approval for this investigation was unnecessary because it only involved standard clinical practice. The study is not a clinical trial; therefore, the registration number is not reported. The data of the study are available. Informed consent was acquired from all enrolled patients before inclusion in the study. There is no material reproduced from other sources. There is no source of extra-institutional funding from commercial sources.

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ORIGINAL PAPER

FUNCTIONAL UROLOGY

Efficacy and safety of photoselective vaporization of the prostate using the Greenlight XPS 180W laser and simple prostatectomy for high-volume prostate hypertrophy: a comparative analysis

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Introduction This study aimed to compare the safety and efficacy of treatment using simple prostatectomy (SP) and using photoselective vaporization of the prostate (PVP) with a 180W GreenLight XPS laser in patients with high-volume prostate hypertrophy.

Material and methods The study included 120 patients with LUTS symptoms caused by prostatic enlargement of more than 80 ml; 79 patients were treated with SP, while 41 were treated with PVP. The analysis included subjective the International Prostate Symptom Score (IPSS) and Quality of Life (QoL), and objective (Qmax), (Qave), and post-void residual volume (PVR) parameters before treatment and at an average of 38 months after surgical treatment. Early and late adverse effects and length of hospitalisation were assessed. Complication reports were performed according to the modified Clavien-Dindo system.

Results The analysis independently showed the effectiveness of both methods. Subjective parameters (IPSS, QoL), showed no significant differences. Patients treated with SP scored slightly better on objective parameters (Qmax, Qave, and PVR). Analysis of adverse effects and hospitalisation time were more favourable after PVP.

Conclusions SP and PVP were found to be comparable and highly effective in treating benign prostatic hyperplasia in terms of IPSS and QoL. Patients treated with the SP method obtained slightly better results of objective parameters such as Qmax, Qave, and PVR. Compared with SP, PVP has a more favourable safety profile.

Key Words: minimally invasive ‹› benign prostatic hyperplasia (BPH) ‹› greenlight 180W XPS laser ‹› PVP ‹› surgical treatment ‹› safety profile ‹› lower urinary tract symptoms (LUTS)s ‹› simple prostatectomy ‹› C-D Clavien-Dindo Classification System

INTRODUCTION

Modern therapeutic technology is rapidly evolving, with particular focus on the active development of minimally invasive methods for treating patients with benign prostatic hyperplasia (BPH). This has led to the systematic introduction of more innovative technologies into everyday life. The same is true for photoselective vaporization of the prostate (PVP).

The introduction of the Greenlight 180W XPS next-generation laser, which utilizes increased power

by using advanced fibre technology, has significantly improved treatment results. However, given the high power of the device, it is crucial to evaluate the safety of this new method.
Surgical treatment of BPH with a volume greater than 80 ml involves the removal of the prostatic adenoma using an open method – simple prostatectomy (SP) – with either a transvesical or prevesical access. Absolute indications for surgical treatment of lower urinary tract symptoms (LUTS) in patients with BPH are mainly recurrent urinary retention, bladder stones, haematuria, recurrent urinary tract infections (UTI), and urinary stasis with or without comorbid renal failure during subvesical obstruction. In addition, patients whose LUTS worsens despite pharmacological treatment, whose quality of life deteriorates steadily, and those who cannot tolerate pharmacotherapy are qualified for surgical treatment [1]. This study aims to determine the effectiveness of BPH treatment with SP and PVP treatment and with the GreenLight XPS laser, and to compare the safety profiles of both methods.
The purpose of this work included the following:
To perform a comparative analysis of the efficacy and safety of SP and PVP GreenLight XPS treatment in patients with BPH.
To perform a comparative evaluation of subjective parameters extracted from the International Prostate Symptom Score (IPSS) and Quality of Life (QoL) questionnaires.
To comparatively evaluate objective parameters on the basis of the results of uroflowmetry studies involving the analysis of parameters, including Qmax, Qave, and PVR.
To perform a comparative evaluation of the side effects and complications in patients undergoing BPH treatment using both methods.
Complication reports were performed according to the modified Clavien-Dindo Classification System, which was published in 2004, was recommended in 2012, and was validated in 2017 by many scientific societies of urology for post-operative complications reports. It is a simple and objective diagnostic tool for the postoperative condition of patients. This modified system is divided into 7 classes, which are presented below [2, 3, 4].
Grade I: Any deviation from normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or interventional radiology. The accepted therapies are drugs such as antiemetic, antipyretics, analgesics, diuretics, and electrolytes, as well as physiotherapy.
Grade II: Complications requiring pharmacological treatment with drugs other than those used in Grade I complication (including haematuria requiring blood transfusion)
Grade III: Complications requiring surgery, endoscopy, or interventional radiology
Grade IIIa: Intervention carried out under any form of anaesthesia other than general anaesthesia (including performing a cystostomy)
Grade IIIb: Intervention performed under general anaesthesia
Grade IV: Life-threatening complications (including central neurological complications)
Grade IVa: Dysfunction of a single organ, including renal failure supported by dialysis
Grade IVb: Multiple organ dysfunction with intensive care unit admission
Grade V: Death of the patient

MATERIAL AND METHODS

The present study used retrospectively collected data including the medical histories of patients operated from 1 January 2012 to 31 December 2017, as well as the results of postoperative examinations performed during the observation period.

Study design and participants

The study participants include patients treated for BPH at 2 centres: patients in the Department of Urology, Oncological and Functional Urology of the Military Institute of Medicine – National Research Institute, who received treatment using SP and a GreenLight XPS 180W PVP, and patients treated using SP during the same period at the Department of Urology of St. Padre Pio Regional Hospital in Przemyśl. The study included 79 patients who underwent SP and 41 patients who underwent PVP. Patients treated with the aforementioned methods were then followed up for an average of 38 months after the procedure. Patients were eligible for both PVP and SP according to similar indications, i.e. patients with increased LUTS, caused by an enlarged prostate measuring more than 80 ml on ultra-sound, and others in whom treatment methods did not produce the expected favourable results. All eligible patients, in the preoperative period, were examined according to the recommendations of the European Association of Urology (EAU). The study centred around medical history, physical examination, and laboratory and imaging studies. For the purposes of this study and analysis, each patient underwent an ultrasound examination prior to surgical treatment, with a focus on prostate volume, and patients were included in the study on this ba-

sis. During the medical interview with the patient, the nature and severity of LUTS was assessed. The patients were presented with all therapeutic options related to the treatment of BPH. An integral part of the patients' examination was the completion of an IPSS and QoL questionnaire by each patient who did not experience urinary retention.

A digital rectal examination (DRE) of the prostate was performed, as well as a panel of standard tests necessary to perform the procedure under anaesthesia. In addition, tests were ordered as part of the evaluation of prostatic and urinary tract disorders: prostate-specific antigen (PSA) levels, microbiological and general urinalysis, and evaluation of renal function and haemoglobin levels, as well as ultrasound evaluation of the upper urinary tract with calculation of prostate volume (Pvol) and urine volume retained after micturition (post-void residual volume – PVR) were assessed.

Prior to surgical treatment, each patient underwent a uroflowmetry examination. This examination was waived before surgery only in patients who had urinary retention, because in this group, ad hoc protection of the urinary tract with a Foley catheter was used. This group included 25 patients who subsequently underwent adenomectomy and 4 patients in the PVP group. Uroflowmetry is one of the basic tests used in the diagnosis of lower urinary tract abnormalities. It is a completely painless, non-invasive, short, and simple to perform test. The volume of urine expelled per unit time was measured, including the rate of maximal urethral flow (Qmax) and the average rate of urethral flow (Qave). The volume of urine retained after micturition (PVR) was then assessed using ultrasound.

Bacteriuria can increase the risk of infection during medical procedures. An especially important procedure was the identification of bacteriuria before the planned procedures to reduce the risk of infectious complications. Patients qualified for surgery, who were found to have a urinary tract infection in the laboratory tests performed, were separated from the respective patient groups. If an acute urinary tract infection was found, the decision to perform surgery was postponed until the patient was successfully treated. The patients were treated using the appropriate pharmacotherapy according to the urine culture result obtained. This group comprised 10 patients who underwent SP and 3 patients who underwent PVP. It should also be noted that a negative urine culture is not always an indicator of the absence of bacteria, because the lower genitourinary tract is colonized by microflora belonging to the microbiome.

In the group of patients qualified for the study, a separate group also included patients who experienced urinary retention. In this group, no uroflowmetry examination was performed before the procedure. Because the urinary tract was secured with a Foley catheter, in this group of patients, in addition to the routinely performed DRE tests, the following were performed: PSA tests, urinalysis and determination of blood creatinine levels, and transabdominal ultrasound (TAUS) with assessment of the volume of the prostate and bacteriological examination of the urine, with particular attention to the antibiotic sensitivity of the bacteria found.

Before surgery, if a positive urine bacteriological culture was obtained, antibiotic therapy was administered, and hospitalisation was postponed for approximately 2 weeks. In the preoperative and perioperative period, they were administered antibiotic therapy according to the antibiogram obtained. Furthermore, these patients underwent additional bacteriological tests after the surgical procedure.

The next group identified from among those qualified for the study were patients with abnormalities on DRE examinations and/or patients who had an increase in serum PSA levels, and who underwent additional testing due to suspected prostate cancer. Based on this, these patients underwent transrectal ultrasound (TRUS) followed by a multisite core biopsy performed with a Tru-Cut needle (18 G) under TRUS guidance (TRUScoreBx).

The evaluation scheme for groups of patients undergoing surgical treatment for BPH is shown in Figure 1.

During follow-up visits, all patients who underwent PVP using the 180W GreenLight XPS laser and SP received a comprehensive evaluation, including uroflowmetry (to measure urethral flow) and ultrasound of the prostate. Additionally, urine retention after micturition was evaluated, along with laboratory tests, such as PSA and general urinalysis. Patients also completed the IPSS questionnaire and the QoL questionnaire, while possible complications of the treatment were assessed.

A flow chart showing the examination of patients who were eligible for surgery is shown in Figure 2.

Surgical methods

Photoselective vaporization of the prostate – surgical procedure scheme

Laser vaporization of the prostate is performed using a device that uses a lithium triborate (LBO) crystal, which emits a 532-nm wave with a power of 180 watts (i.e. an XPS laser). An Nd-YAG laser

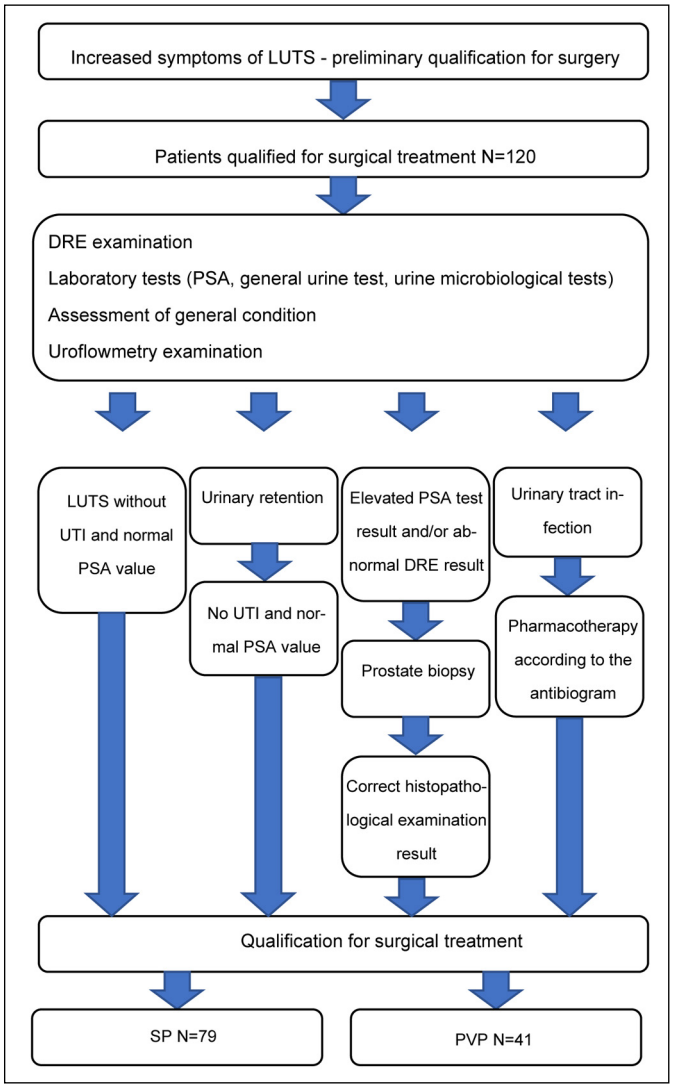

Figure 1. *Scheme for evaluating groups of patients receiving benign prostatic hyperplasia surgery.*

DRE – digital rectal examination; LUTS – lower urinary tract symptoms; N – number of patients; PSA – prostate-specific antigen; PVP – photoselective vaporization of the prostate; SP – simple prostatectomy; UTI – urinary tract infections

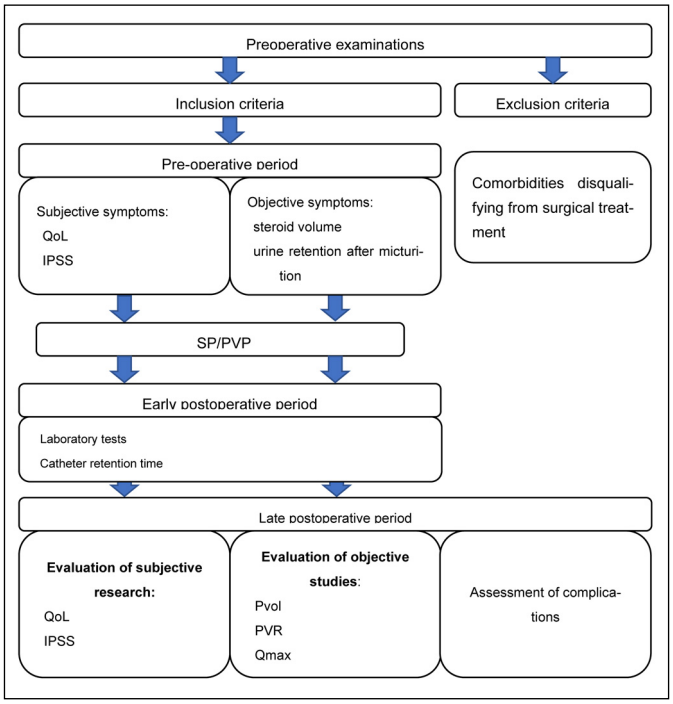

Figure 2. *Study pattern of patients undergoing surgical treatment for benign prostatic hyperplasia between 2012 and 2017.*

IPSS – International Prostate Symptom Score; Qmax – maximal urethral flow; QoL – quality of life; Pvol – prostate volume; PVP – photoselective vaporization of the prostate; PVR – post-void residual volume; SP – simple prostatectomy

wave of 1064 nm is passed through this crystal. This wave is selectively absorbed by haemoglobin; furthermore, it is transmitted through water and penetrates cells without energy loss. Absorption of this wave leads to the immediate removal of glandular tissue by rapid photothermal vaporization of heated intracellular water. Hence the name photoselective vaporization of the prostate [5].

In addition, this laser features an innovative system for controlling the emitted energy from the fibre. GreenLight™ MoXy™ delivers laser light to the tissue with a maximum power of 180 watts and a wavelength of 532 nm during PVP treatment. The MoXy™ Liquid Cooled Fibre with Active Cooling Cap™ technology used in this device ensures the flow of fibre salt solution around the fibre, which has a cooling effect and minimizes devitrfication of the fibre tip. The device is equipped with a vision track with a light source, camera, monitor, and a 24F continuous flow rigid cystoscope.

Simple prostatectomy – scheme of operational procedure

The SP procedure with various modifications (including Hryntschak) is still commonly per-formed using various types of haemostatic nipples. Extirpation of the adenoma is performed prepubescently by inserting the index finger into the prostatic portion of the urethra, after which the finger is moved to its anterior wall to break the prostatic urethra. By moving the finger laterally, the lateral lobes of the adenoma are separated from the prostatic capsule. Afterwards, a Foley or Dufour catheter (22–24 F) is inserted into the bladder through the urethra, and a temporary haemostatic suture is also placed to control frequent bleeding from the site of the prostatic adenoma. The next step is to insert a cystostomy catheter into the bladder. After controlling haemostasis, the urinary bladder is sutured in 2 layers using a continuous suture.

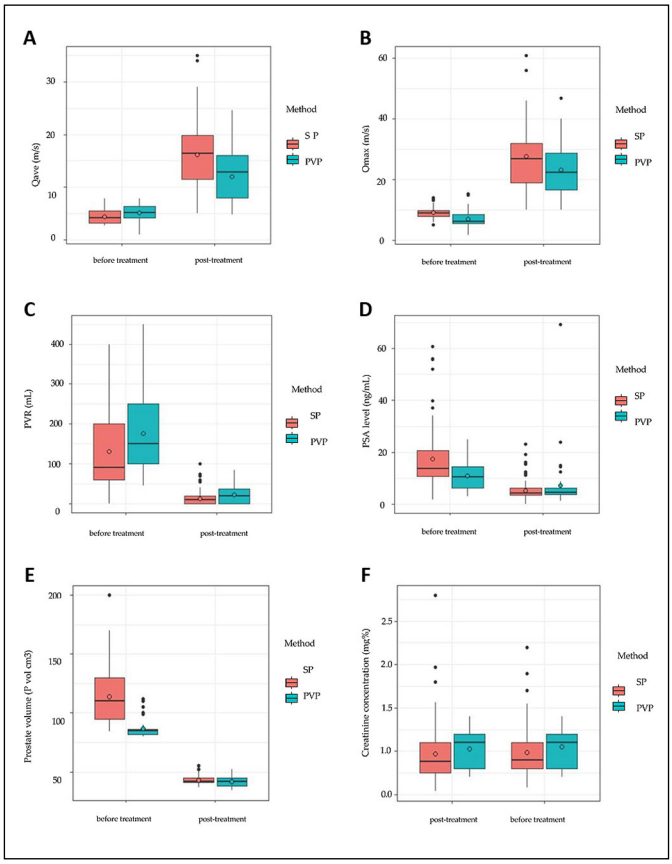

Figure 3. *Plot of mean, median, and first and third quartile values for objective parameters by SP and PVP 31 treatment method and time of measurement (before and after treatment):* **A** *– average flow rate (Qave);* **B** *– maximum flow rate (Qmax);* **C** *– post-voiding residual urine (PVR);* **D** *– PSA level;* **E** *– prostate volume (P vol);* **F** *– Creatinine concentration.*

Statistical analysis

For quantitative characteristics, one-way analysis of variance (ANOVA) was used as a method to evaluate the effectiveness of treatment methods. For objective parameters (Qmax, Qave, PVR, prostate volume, and creatinine and PSA concentrations), the analysis of the effectiveness of the 2 BPH treatment methods, as well as the comparative analysis of these methods, was performed using a one-factor ANOVA. When evaluating the effectiveness of the application of each treatment method, i.e. SP or PVP GreenLight XPS, the ranking factor was the time of measurement of the analysed parameters before and after the application of treatment. Statistically significant differences between group values were determined based on a p-value of less than 0.05. Polychoric correlation analysis was used to assess the co-variance of quantitative characteristics expressed as ordinal variables (this applies to IPSS and QoL scores). Underlying the use of the polychoric correlation index is the assumption that both parameters, IPSS and QoL, are continuous variables that have been "simplified" to an ordinal scale. A given subjective parameter (IPSS, QoL) and the time at which it was measured (before and after treatment) were put to test. The higher the absolute value of the correlation index, the stronger the implied relationship between a given subjective parameter and time. If the correlation index had a negative value, it meant that after treatment with a particular method, the value of the analysed subjective parameter decreased after the use of the given approach. If the correlation index had a positive value, the treatment would be accompanied by an increase in the value of this parameter.

RESULTS

In the present study, the parameters that support the effectiveness of the method were evaluated for an average of 38 months after treatment, which was a sufficient duration that allowed for an effective and accurate assessment of distant treatment results. Patients had their LUTS complaints assessed using the IPSS and QoL sheets. On the other hand, functional evaluation of the lower urinary tract was performed using uroflowmetry (Qmax, Qave), and assessment of post-voiding residual of urine was performed using ultrasound.

The patients' age range in group 1 (SP) was 51 to 86 years, with a mean age of 69.5 years. In group 2 (PVP), the age range was 53 to 78 years, with a mean age of 67.4 years. Preoperative IPSS values in the SP group ranged from 20 to 33, with an average of 26.5, and in the PVP group from 12 to 35, with an average of 22.5. Before treatment, quality of life was scored by SP-treated patients at 4 to 6 points, with an average of 5 points, and by PVP-treated patients at 3 to 6 points, with an average of 5 points.

In the group of patients before PVP treatment, the averaged uroflowmetric parameters were as follows: Qmax: 7.14 ml/s; Qave: 5.11 ml/s; and PVR: 184.34 cm^3, definitively indicating clinically important urinary outflow abnormalities associated with the existence of a subvesical obstruction in the course of BPH. The objective findings obtained confirm the subjective IPSS and QoL results. In patients who qualified for SP, preoperative results also indicated significant urinary outflow obstruction: Qmax: 9.17 ml/s; Qave: 4.43 ml/s; and PVR: 130.52 cm^3. These data are presented pictorially in Figures 3A, B, C.

In the ultrasound examinations performed, Pvol in the SP group ranged from 84 cm^3 to 200 cm^3, mean:

Table 1. *Parameter values before and after treatment of patients with simple prostatectomy and photoselective vaporization of the prostate methods*

Variable	Simple prostatectomy				PVP			
	Before treatment		After treatment		Before treatment		After treatment	
	average	dev. std.	average	dev. std.	average	dev. std.	average	dev. std.
IPSS (points)	26.47	2.72	6.22	1.89	22.51	4.99	7.41	5.47
QoL (points)	4.95	0.58	1.30	0.61	4.76	0.86	1.63	0.97
Qmax (ml/s)	9.17[1]	1.86[1]	27.86	10.27	7.14[2]	2.88[2]	23.28	9.17
Qave (ml/s)	4.43[1]	1.39[1]	16.13	5.80	5.11[2]	1,76[2]	12,05	4.69
PVR (ml)	130.52[1]	99.26[1]	13.42	20.04	184.34[2]	115.47[2]	21.98	22.70
Volume of the prostate (cm^3)	113.85	21.24	43.24	4.09	86.49	7.71	41.73	4.25
Creatinine concentration (mg%)	0.99	0.28	0.97	0.35	1.05	0.21	1.03	0.20
PSA level (ng/ml)	4.38	2.95	1.33	1.00	2.75	1.39	1.79	2.70

[1] n = 52, [2] n = 37
IPSS – International Prostate Symptom Score; Qave – average rate of urethral flow; Qmax – maximal urethral flow; QoL – quality of life; PSA – prostate-specific antigen; PVP – photoselective vaporization of the prostate; PVR – post-void residual volume

Table 2. *Mean and standard deviation values of parameters (variables) for the early postoperative period for simple prostatectomy and photoselective vaporization of the prostate methods*

Variable	SP		PVP	
	average	dev. std.	average	dev. std.
Duration of hospitalisation (days)	9.49	0.90	2.27	0.63
Catheterisation time (days)	8.90	0.71	1.80	0.64
Creatinine concentration (mg%)	0.97	0.35	1.03	0.20
Haemoglobin concentration (g/dl)	12.98	1.29	14.34	0.81

PVP – photoselective vaporization of the prostate; SP – simple prostatectomy

Table 3. *Results of one-way analysis of variance for simple prostatectomy method (before and after treatment)*

Variable	Average value before treatment	Average value after treatment	p-value
Qmax (ml/s)	9.17[1]	27.86	<0.01
Qave (ml/s)	4.43[1]	16.13	<0.01
PVR (ml)	130.52[1]	13.42	<0.01
Pvol	113.85	43.24	<0.01
Concentration creatinine (mg%)	0.99	0.97	0.658
PSA level (ng/ml)	4.38	1.33	<0.01

[1] n = 52
Qave – average rate of urethral flow; Qmax – maximal urethral flow; PSA – prostate-specific antigen; PVR – post-void residual volume; Pvol – prostate volume

113.85 cm^3 (range, 80–112 cm^3), while the average volume in the PVP group was 86.49 cm^3 (Fig 3E).

Table 1 shows the mean values of the parameters observed before and after treatment, which were analysed for the SP and PVP methods, respectively. Testing of objective parameters including Qmax, Qave, and PVR was not performed before treatment in patients with urinary retention (AUR).

The distribution of the values of the analysed parameters is shown in Figure 3.

The average duration of hospitalisation of patients treated with SP was 9.5 days (8–11 days), while patients who underwent PVP stayed in the hospital for an average of 2.3 days (1–4 days). In the SP group, catheterisation time ranged from 8 to 10 days (average, 8.9 days), while in the PVP group, it ranged from 1 to 3 days (average, 2.3 days). In the postoperative period, creatinine and haemoglobin levels in SP-treated patients were 0.54–2.8 mg% (mean 0.97) and 9.1–15.2 g/dL (mean 13.0 g/dL), respectively, while in the PVP group they were 0.7–1.4 mg% (mean 1) and 11.8–15.8 g/dL (mean 14.3 g/dL), respectively.

Objective parameters were not studied in the early post-operative period because individual patients may have had an increase in the severity of lower urinary tract symptoms during this time, and they do not reflect the actual condition for comparing the 2 methods. Moreover, dysuric symptoms resolved at an average of 2 weeks after the PVP procedure. The section on the incidence of late complications includes information on the occurrence of recurrent urinary tract infections and the presence of long-lasting dysuric symptoms.

Table 4. *Polychoric correlation results for subjective parameters in patients treated with simple prostatectomy (before and after treatment)*

Variable	The value of the correlation coefficient
IPSS	-0.998
QoL	-0.998

IPSS – International Prostate Symptom Score; QoL – quality of life

Table 5. *Results of one-way analysis of variance for the photoselective vaporization of the prostate method (before and after treatment)*

Variable	Average value before treatment	Average value after treatment	p-value
Qmax	7.14[2]	23.28	<0.01
Qave	5.11[2]	12.05	<0.01
PVR	184.34[2]	21.98	<0.01
Pvol	86.49	41.73	<0.01
Creatinine concentration (mg%)	1.05	1.03	0.676
PSA (ng/ml) level	2.75	1.79	<0.05

[2] n = 37
Qave – average rate of urethral flow; Qmax – maximal urethral flow; PSA – prostate-specific antigen; PVR – post-void residual volume; Pvol – prostate volume

Table 6. *Polychoric correlation results for subjective parameters in photoselective vaporization of the prostate treated patients (before and after treatment)*

Variable	The value of the correlation coefficient
IPSS	-0.911
QoL	-0.994

IPSS – International Prostate Symptom Score; QoL – quality of life

The first stage of the analysis evaluated the effectiveness of treatment methods.

Simple prostatectomy: assessment of the effectiveness of the treatment

The results of the analysis, which are indicated in Table 3, suggest that there were significant differences ($p < 0.05$) in the mean values of the parameters before and after the application of SP treatment to patients. The exception is the result of creatinine, for which no significant differences were noted before and after the treatment (Fig. 3F).
Regarding qualitative traits, the relationship between pre-treatment and post-treatment SP parameter scores was assessed using the value of the polychoric correlation coefficient. Initially, the scores of the IPSS questionnaire were 26.5; however, this decreased to 6.2 at a later observation time after the implementation of treatment, which indicates a significant improvement, in terms of subjective symptom entrainment. Before treatment, the average QoL score was 4.9, while at the distant follow-up visit after the implementation of treatment, it improved significantly to an average of 1.3. Following the SP procedure, the observed change in the value of each evaluated parameter led to the conclusion of the beneficial effect of this surgical method on the patients' urination conditions.
The results shown in Table 4 indicate a negative correlation between the values of subjective parameters (IPSS and QoL) and the time of their measurement (before and after treatment). Among SP-treated patients, IPSS and QoL questionnaire scores were significantly lower after treatment compared to before treatment.

Table 7. *Results of one-way analysis of variance for selected objective parameters in patients treated with simple prostatectomy or photoselective vaporization of the prostate*

Variable	Average value after SP treatment	Mean value after PVP treatment	p-value
Qmax (mL/s)	27.86	23.28	<0.05
Qave (mL/s)	16.13	12.05	<0.01
PVR (mL)	13.42	21.98	<0.05
PSA (ng/mL) level	4.38	1.79	0.178

Qave – average rate of urethral flow; Qmax – maximal urethral flow; PSA – prostate-specific antigen; PVP – photoselective vaporization of the prostate; PVR – post-void residual volume; SP – simple prostatectomy;

Table 8. *Polychoric correlation results for subjective parameters in patients treated with simple prostatectomy and photoselective vaporization of the prostate (after treatment)*

Variable	Value of the correlation coefficient
IPSS	0.026
QoL	0.221

IPSS – International Prostate Symptom Score; QoL – quality of life

Photoselective vaporization of the prostate: evaluation of the effectiveness of the treatment

As with the application of SP treatment, the results of the analysis show that there were significant differences in the mean values of parameters before and after PVP treatment. The exception is the creatinine results, for which there were no significant differences before and after treatment. IPSS questionnaire scores also decreased significantly from a baseline of 22.5 to 7.4 in the late period. This indicates a sig-

nificant improvement with regard to the symptoms of LUTS that were reported by patients.
Before treatment the average QoL score was 4.8, while in the post-treatment period this score improved to an average of 1.6. The change in the value of each evaluated parameter, i.e. a decrease in IPSS, QoL, and PVR, and an increase in Qmax and Qave, confirm the beneficial effect of the treatment method on urination. These results indicate that the presence of a sub-bladder obstruction was confirmed in patients before applying the treatment; hence, the application of the PVP method influenced its resolution.
The results shown in Table 6 indicate a negative correlation between the values of subjective parameters (IPSS and QoL) and the time they were measured (before and after treatment). Furthermore, among PVP-treated patients, the IPSS and QoL questionnaire scores were significantly lower after treatment than prior to treatment.
The change in the value of each evaluated parameter, i.e. a decrease in IPSS, QoL, and PVR, and an increase in the values of Qmax and Qave, suggest the beneficial effect of the treatment method on urinary conditions and on any symptoms related to this process. The results, which were obtained through statistical analyses, clearly indicate that the presence of a sub-bladder obstruction in patients prior to the application of treatment; furthermore, the introduction of the PVP method influenced its resolution.

Comparative evaluation of the effectiveness of simple prostatectomy and photoselective vaporization of the prostate

It is extremely important to evaluate the comparative effectiveness of the 2 treatment methods analysed. The evaluation was made on the basis of qualitative parameters, including IPSS and QoL, as well as quantitative parameters, namely, Qmax, Qave, PVR, and PSA.
Additionally, after both forms of treatment, there was a significant improvement in urethral flow, as well as a decrease in the PVR. Considering the average values of quantitative parameters, such as Qmax, Qave, and PVR, after treatment, the SP method proved to be the better method. The results shown in Table 7 and Fig. 3 indicate some differences in objective parameters (Qmax, Qave, and PVR) depending on the treatment method used. The Qmax and Qave parameters were lower and the PVR parameter was higher for patients treated with PVP compared to those of patients treated with SP. However, there were no significant differences in PSA concentrations between the 2 treatment methods (Table 7 and Figure 3D). Regarding qualitative characteristics, the correlation between parameter scores after SP and PVP treatment indicated that there were no clear differences in IPSS and QoL scores among patients treated with SP and PVP.
Regarding qualitative traits, the relationship between parameter scores after SP and PVP treatment was assessed based on the value of the polychoric correlation coefficient. The relationship was tested between a given subjective parameter (IPSS, QoL) and the treatment method (SP, PVP).
The results shown in Table 8 indicate a low positive correlation between the values of subjective parameters, IPSS and QoL, and the method of treatment used. Hence, there were no clear differences in IPSS and QoL questionnaire scores among patients treated with SP and PVP.
The above results demonstrate several conclusions. First, regarding baseline parameters after both forms of treatment, there was a significant improvement in urethral flow, as well as a decrease in the volume of urine that lingered after micturition (PVR). Second, due to quantitative parameters, such as Qmax, Qave, and PVR, better average results were obtained after SP treatment.

Comparative evaluation of photoselective vaporization of the prostate and simple prostatectomy in relation to adverse effects

An important issue representing another objective of the analysis was the comparison of the 2 surgical methods in the context of certain side effects. After each procedure, we analysed the decrease in haemoglobin (Hb) concentration in the patients' blood, which was associated with intra- and postoperative bleeding, and consequently we also determined the frequency of red blood cell concentrate (RBC) transfusions.
For comparative evaluation of PVP and SP values obtained before surgery, haemoglobin levels in patients treated with SP and PVP were 13.9 g/dL and 14.6 g/dL, respectively. After surgery, the above values were 13.0 g/dL and 14.3 g/dL, respectively.
The rate of postoperative complications treated with the SP method according to C-D was 24%. Complications in this area included, in particular, infections, haematuria and anaemia. Complications of grade II C-D occurred in 14 (18%) patients, and 9 (10%) in grade I. All the above-mentioned complications were managed conservatively with medication and blood transfusion. No C-D complications were observed in higher grades.
The rate of postoperative complications treated with PVP according to C-D was 17.5%. Complications in this area included, in particular, increase in body

temperature, transient haematuria, and anaemia. Complications of grade II C-D were not observed, while 4 (10%) had grade I complications. All the above-mentioned complications were managed conservatively with the administration of medications. No C-D complications were observed in higher grades. No patients required a re-intervention because of bleeding (Clavien-Dindo >IIIa) in the PVP group.
The results of comparative statistical analysis proved that the average haemoglobin concentration was significantly lower in patients who were treated with the SP method than in those treated with the PVP method; therefore, blood loss was statistically higher in patients who underwent SP ($p < 0.01$). In addition, 14 SP-treated patients (18% of the study group) were accompanied by the need for blood clot transfusion. In contrast, PVP treatment did not require the transfusion of the CRC to any patient after the procedure.

DISCUSSION

In the last century, SP has become the primary treatment for BPH. It was considered the gold standard for the treatment of this condition. Although, at the turn of the century, significant progress was made in the development and introduction of minimally invasive techniques for the treatment of BPH, open access approaches are still widely used, especially for large adenomas [6, 7, 8]. Although until recently it was recognized that the limit of eligibility for con-fluence between transurethral surgery and open prostatectomy remained a matter of debate, including in the AUA and EAU guidelines for the treatment of lower urinary tract symptoms in men, the open method is still recommended for adenomas with volumes >80–100 ml [9, 10]. More recently, this limit for transurethral access has been questioned in several studies, due to the increasing use of laser treatments [11].
Despite the wide spread use of "gold standard" treatments including transurethral electroresection (TURP) with bipolar (BiTURP) and laser procedures, such as PVP and holmium laser enucleation (HoLEP), or thulium laser (TuLEP), which are considered by some to be the best treatment option for BPH regardless of prostate size [12 ,13], SP remains the procedure of choice for patients with glands that are too large for safe endoscopic resection [9, 10].
SP is undoubtedly a treatment option that significantly reduces LUTS symptoms [14–18]. In a comparative randomized trial, Meyhoff et al. showed that SP was well accepted by patients, as only 9% of those who underwent this procedure were dissatisfied with the treatment outcomes compared to 15% of those who underwent TURP, which is considered the "gold standard" for treating BPH [19, 20, 21]. Tubaro et al. examined patients who underwent urodynamic evaluation 12 months after SP [16]. The study showed a significant reduction in symptoms in terms of assessed IPSS parameters, QoL, Qmax, and PVR. Approximately 84% of patients reported subjective improvement in QoL. None of the patients had a value greater than 3, with a mean value of 0.2. In this study, 60% of patients reported no LUTS after treatment, and 96.9% of patients had a flow rate greater than 15 ml/s one year postoperatively [16]. Varkarakis et al. confirmed these data in another study [17]. Additionally, another study retrospectively evaluated 151 patients who underwent SP for BPH (adenoma mass greater than 70 g) 5 years postoperatively [16]. The study showed significant improvement after 8 to 12 months of follow-up, as shown by an increase in Qmax, a significant re-duction in PVR a decrease in LUTS symptoms, as well as improvements in QoL, which were statistically significant 12 months after surgery and did not change significantly after longer follow-up (mean 41.8 months). Unfortunately, open surgery is associated with a higher rate of complications compared to endoscopic procedures. Complications related to wound healing or the occurrence of bladder-skin fistula occur in 0.4–4% of patients in the immediate postoperative period [17, 22]. The duration of hospitalisation after the procedures performed was not significantly different; the duration of hospital stay is also usually longer with open procedures. According to Tubaro and Varkarakis, the average duration of hospitalisation was 6–10 days, and this is related to the period of catheterization (a median of 5 days) [16, 17, 22].
PVP is a technique that is increasingly used in urology. Studies have shown the effectiveness of this treatment method in BPH. Published studies indicate a reduction in bladder catheterization time and hospitalisation time, as well as the possibility of using this method in patients treated with antiaggregants and/or anticoagulants. Considering the parameters mentioned, IPSS and Qmax improved significantly and were compared in a prospective study with the group treated with SP. The result of treatment, in terms of subjective evaluation, was satisfactory in both groups, and as emphasized, PVP is an alternative method of treating BPH in patients with large adenomas. Rajbabu et al. noted that there were no major complications or the need for blood transfusions, confirming the safety and efficacy of laser vaporization of large volume prostates [13]. A study by Raimbault et al. [23] compared data collected retro-

spectively for the SP-treated group with data from a prospective analysis for the PVP group with adenomas weighing more than 80 g. The patients were followed for one year. Although the guiding purpose of the study was to compare the economic aspects of the 2 methods, it also presented data showing their efficacy. Forty-one patients in the SP group and 53 in the PVP group treated with a GreenLight laser (LBO) were evaluated. The mean length of stay was significantly shorter in the PVP group than in the SP group (3.0 ±1.0 days vs 10.4 ±4.0 days; p <0.001). Reoperations after one year were less frequent in the PVP group than in the SP group (1.9% vs 19.5% p <0.001). Furthermore, patients in the SP group had a higher mean prostate weight (129 vs 110 g) and higher mean PSA values (11.4 vs 8.7 ng/ml). The treatment duration was comparable for both methods (100.4 ±29.5 min for the group that underwent SP vs 104.9 ±47.8 min for the PVP group). The study also considered the number of patients treated with antiaggregants and/or anticoagulants. In the open procedure group, 21.9% of patients (9/41) were administered antiplatelet drugs, and 4.9% (2/41) of patients received anticoagulants. All patients in this group discontinued these drugs preoperatively. In the PVP group, 40.4% of patients (21/52) used antiplatelet drugs, and 3 of the patients continued treatment during surgery. The reoperation rate (immediate and late) was 19.5% in the suprapubic adenomectomy group and 1.9% in the PVP group (p <0.001) [23]. On the other hand, in a comparative analysis of BPH treatments using PVP and SP in patients with prostate adenomas of over 80 g, Raimbault and Watt observed that the average length of stay was significantly shorter in the group of patients treated with PVP, and this significantly reduced treatment costs [23]. The comparison also examined the costs associated with the procedure, including hospitalisation costs. The PVP-treated patient group had a significant reduction in hospitalisation and bladder catheterization time maintained for approximately 24 hours; moreover, the procedure could be used in patients treated with antiaggregants and/or anticoagulants [23]. Although the cost of purchasing a generator and fibre is significant, given the short hospitalisation time, the PVP procedure is more economical. According to Rajbabu and Chandrasekar, the duration of the procedure was similar in both. Patients treated with the open procedure experienced more bleeding than those in the PVP group, which was confirmed by the changes in haemoglobin levels before and after the procedure. This resulted in the need for blood transfusions in 15 patients who were treated with open surgery, while patients who underwent PVP did not require transfusions. Furthermore, another advantage of PVP was the rate of total reoperation (immediate and late), which was 19.5% in the SP-treated group versus 1.9% in the PVP group (p <0.001). PVP is the dominant management strategy because it reduces the number of reoperations while reducing the immediate cost of surgery compared to open surgery. Moreover, PVP is a technique that is increasingly used in urology, and conducted analysis has shown its effectiveness in reducing symptoms of BPH when compared to that of TURP [23, 24, 25]. This study confirms the safety and efficacy of the laser in large-volume sterile vaporization. No major complication or the need for transfusion was found during or after the procedure [13].

There are few reports on the comparative evaluation of the effectiveness of the treatment of prostate adenomas with a volume of more than 80–100 ml using the PVP method with the XPS 180 W laser and the SP surgical method, which is still in use. The large size of the compared patient groups and the study design used for the analysis made it possible to obtain reliable results. Undoubtedly, the advantage of this study is the relatively long follow-up period, at an average of 38 months. The validated questionnaires for assessing LUTS (IPSS – International Prostate Symptom Score, ICIQ-MLUTS – International Consultation on Incontinence Ques-tionnaire, and DAN-PSS – Danish Prostate Symptom Score) meet the recommendations for diagnostic tools in benign prostatic hyperplasia. Based on the above questionnaires, it is possible to estimate the severity of complaints and determine the predominant ones, which makes them valuable tools in monitoring patient outcomes [17, 18].

Analysis of the objective parameters, which were obtained using uroflowmetry examination in the period before the treatment and an average of 38 months after the treatment, including maximum urethral flow, average urethral flow, and PVR, shows that both in the case of SP and PVP there was a significant improvement in their values, with particular emphasis on the improvement of urinary conditions after treatment and the abolition of symptoms of urinary out-flow obstruction.

Regarding IPSS and QoL, as well as Qmax, Qave, and PVR, the study conducted indicates that significant improvements were obtained regardless of the treatment method used. This study also conducted a comparative evaluation of the described treatment methods, using the same subjective and objective parameters. Considering their mean values after treatment, more favourable, results

were obtained after SP. The Qmax and Qave parameters were lower, and the PVR parameter was better, for patients treated with SP compared to those treated with PVP. In contrast, there were no clear differences in IPSS and QoL questionnaire scores among SP- and PVP-treated patients.

The study clearly indicates that the new treatment method of PVP has measurable results and is as effective as SP (which has been used for many years) in the treatment of BPH.

It is worth noting that an additional element of the above study was the evaluation and comparison of side effects and complications that occurred in patients treated with both methods. Accordingly, factors that occur immediately after performance of the procedure and at a later time were evaluated. Factors that were analysed and occurred immediately after the procedure focused on post-operative bleeding, haemoglobin levels, the need for transfusions of blood products (CRP) after the procedure, and the occurrence of infectious symptoms.

It has been shown that there are important differences regarding the frequency of intraoperative and postoperative bleeding, and in the reduction in haemoglobin concentration in patients who require blood transfusion in exceptional situations. The comparative results obtained prove that the average haemoglobin concentration was significantly lower in patients who were treated with SP than in those treated with PVP, while blood loss was statistically higher in patients who underwent SP. In addition, after treatment with SP, approximately 18% of the study group required transfusion of blood cells. In contrast, treatment with the PVP method did not create a need for transfusion of the CRC for any patient after the procedure.

The results obtained in the study on postoperative assessment of prostate adenoma using both methods according to the Clavien-Dindo classification are similar to the results obtained in other urological trials [26, 27, 28].

In our study the postoperative complications treated with the SP method according to C-D were observed in grade I and II. Immediate complications (18%) were mainly represented by perioperative bleeding with the need for blood transfusion (complication grade II)

Postoperative complications treated with PVP according to C-D were observed in grade I. Complications of grade II C-D were not observed, while 7 (17.5%) had grade I complications. All the above-mentioned complications were managed conservatively with the administration of medications. No C-D complications were observed in higher grades, and no patients required a re-intervention because of bleeding (Clavien-Dindo >IIIa) in the SP and PVP group.

Fever requiring antipyretic drugs was the main cause of grade I complications. This value was influenced by perioperative antibiotic therapy and the identification of urinary tract infections before surgery.

The results obtained are comparable to data presented by other authors [29, 30, 31]. Considering postoperative bleeding, which significantly affects the clinically relevant decrease in haemoglobin concentration and creates the need to supplement blood products, the present analysis confirms previous reports in the literature emphasizing the superiority of PVP over SP in this regard ($p < 0.01$) and showing the greater safety of PVP laser vaporization over SP. The number of patients who are administered anticoagulants for cardiovascular conditions increases every year, and their use is a contraindication to performing SP because they are associated with the risk of serious bleeding complications. The purpose of the above analysis was not to assess the feasibility of performing PVP and the risk of postoperative bleeding in patients receiving anticoagulants and antiaggregants. However, data from the literature on the superiority of PVP over other methods in this regard, including SP, confirms the safety of this method [27, 32, 33].

In a study performed at the Department of Urology, Oncological, and Functional Urology at the WIM in Warsaw, the efficacy of PVP treatment in patients with BPH using the GreenLight XPS, LBO 180W laser was evaluated. A definite improvement in maximum urinary flow rate (Qmax) was observed from 8.9 before treatment to 20.8, 21.4, and 21.2 ml/s after 1, 3, and 6 months, respectively. The IPSS decreased from 23.8 to 8.3, 7.7, and 7.1 points at 1, 3, and 6 months, respectively, while the QoL score decreased from 4.2 to 1.8, 1.7, and 1.5 points at 1, 3, and 6 months, respectively. The authors of the study observed no significant complications or changes in blood parameters (haemoglobin and sodium) during PVP. The most common post-operative complications included transient dysuria and haematuria [34]. Favourable clinical effects of SP in the treatment of patients with BPH were observed, and this study attempts to answer the question of whether the new treatment method, which is based on PVP, is equally effective and whether it can be used as the gold standard in the treatment of BPH on its own.

An undeniable benefit flowing from the use of PVP is the shorter hospitalisation period for patients. The average length of hospitalisation for patients undergoing SP was 9.49 days, while patients who underwent PVP stayed in the hospital for an average of only 2.27 days. This supports the notion that pa-

tients treated with PVP are likely to quickly return to full social and professional activity.
The study's results completely confirm the previously formulated assumptions, recognizing the effectiveness of PVP at almost the same level as SP and identifying its superiority in some respects. Based on these data and premises, it should be concluded that PVP can be used extensively in the treatment of BPH. Additional analysis of side effects associated with both methods confirmed the superiority of PVP over SP in this regard, as already recognized in previous literature reports.

CONCLUSIONS

This study demonstrated the comparable and high efficacy of SP and PVP with the GreenLight XPS 180W in the treatment of patients with BPH. The evaluation of subjective parameters, which were obtained based on the IPSS and QoL questionnaires, also showed high therapeutic efficacy for both methods studied, and there were no statistically significant differences between them.
The results of the statistical analysis showed that patients treated with the SP method had better results in terms of objective parameters, such as the Qmax, Qave, and PVR. However, in terms of the abolition of the symptoms of LUTS and the fact that an improvement in micturition was obtained lastly, both methods should be considered effective in the treatment of BPH. Moreover, this was confirmed in the evaluation of treatment efficacy for each method in terms of objective and subjective results. Furthermore, PVP with the GreenLight XPS 180W had a more favourable safety profile than SP in terms of intraoperative bleeding, urinary tract infection risk, catheterization duration, and hospital stay. This makes it an effective and safe method for treating BPH in high-risk patients who cannot undergo previous treatments.
These results make PVP with the GreenLight XPS 180W an effective and safe method for treating BPH, allowing for the safe expansion of indications and coverage of treatment for patients in risk groups. The low number of complications and side effects, low invasiveness of the method, and short hospital stay enable a faster return to the daily life activities of patients and provide tangible socioeconomic benefits.
The study evaluated the efficacy parameters at an average of 38 months after surgery, which effectively assessed the distant results of the treatment. However, a longer period of observation (e.g. 5–10 years after the procedure) would provide unequivocal confirmation of the long-term persistence of treatment effects. While a comparative analysis may provide further verification, the parameters used in this study based on objective and subjective criteria are sufficient. The literature on the subject indicates that many papers comparing other therapeutic methods for BPH use identical research instruments. Therefore, the results of this study provide an opportunity to confirm the favourable changes occurring in the improvement of objective test results after surgical treatment.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

FUNCTIONAL UROLOGY

Detrusor underactivity in symptomatic anterior pelvic organ prolapse

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Introduction The aim of this study was to assess the detrusor underactivity (DUA) prevalence of females with symptomatic anterior pelvic organ prolapse (POP) and to evaluate the relationship between DUA and POP stage.

Material and methods This was a prospective study recruiting women with symptomatic anterior POP. Patients with symptomatic stage 2–4 POP quantification system (POP-Q) who underwent urodynamics (UD) between January 2018 and April 2021 were included.

Results Data on 330 women (mean age 63.7 ±18.4 years old) with anterior vaginal wall defect were enrolled. Concomitant apical defect (uterine/vaginal vault) requiring surgical correction was diagnosed in 38 women (11.5%). DUA was found in 166 females (50.3%). In DUA women, POP-Q stage 2 was found in 45.2%, stage 3 in 50.9% and stage 4 in 76.5%. Only stage POP-Q stage 4 showed a statistically significant difference between DUA and non-DUA females (p 0.006).

Conclusions In women with symptomatic POP, regardless of the POP-Q stage, the chance of DUA occurrence was high. DUA was diagnosed in approximately half of the women undergoing UD for symptomatic POP, and it was three-fold higher in cases of POP-Q stage 4. Due to the high incidence of DUA in POP-Q 4 stage, it may be advantageous to identify and treat prolapse before they progress to stage 4.

Key Words: pelvic organ prolapse ‹› anterior vaginal wall defect ‹› urodynamics ‹› detrusor underactivity

INTRODUCTION

Diagnosis of female detrusor underactivity (DUA) is challenging due to the lack of specific criteria [1]. The ICS definition of DUA – a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span – does not report any urodynamic (UD) thresholds, and has no numerical cut-offs [2]. How strong a 'normal' detrusor contraction should be and how long it should last are not stated. The prevalence of female DUA ranges from 15 to 53.9%, but these numbers are impacted by the use of non-homogeneous criteria [3]. Little high-quality information is available on DUA rates in women with symptomatic pelvic organ prolapse (POP) and in these patients DUA ranges from 13.3% to 40.9% but, again, this great variability is probably due to the different criteria utilized [4, 5, 6]. Therefore, the actual clinical relevance of female DUA in the general population, and even more so in women with POP, has yet to be defined with certainty. Also, no findings are available on the relation between detrusor impairment and POP stages. Therefore, epidemiological data on the relationship of DUA to POP stages is needed, as investigation into

the relationship between POP with associated DUA and its interaction with lower urinary tract symptoms. This study explored these under researched topics to provide missing epidemiological data.
The aim of the study was to assess DUA prevalence in females with symptomatic POP in a large cohort of candidates for POP surgery, using the four most recognized UD criteria. A second aim was to evaluate the relationship between DUA and POP stage.

MATERIAL AND METHODS

This was a prospective study recruiting women with symptomatic anterior POP, assessed by POP quantification system (POP-Q), undergoing UD between January 2018 and April 2021 in one Tertiary referral Centre [7]. Inclusion criteria were: any symptomatic anterior POP stage ≥2 according to POP-Q system, with or without associated apical/uterus descensus. For symptomatic POP we included all the symptoms related to pop as pelvic discomfort or pain, bulge of tissue or organs, protruding to or past the vaginal opening, sexual difficulties, dyspareunia related to POP, fulness of pressure in vagina, vaginal spotting. Medical and urogynecological history, and UD data were recorded. POP evaluation and staging were performed by 3 specialized urologists (MB, ER, AD).
Due to the lack of standardized UD parameters for female DUA, we classified patients as having DUA if they met at least one of the main criteria reported in the literature: 1) Pdet@Qmax ≤10 cmH_2O and Qmax ≤12 mL/s (Jeong et al, 2012); 2) Pdet@Qmax <30 cm H2O and Qmax <10 mL/s (Abarbanel and Marcus, 2007); 3) Pdet@Qmax <20 cm H_2O and Qmax <15 mL/s and BVE <90% (BVE criteria); 4) Pdet@Qmax + Qmax (Griffiths, 2004) [8–13]. For the above mentioned reasons patients could be included in multiple DUA groups according to the criteria used. The control group (CG) consisted of women with symptomatic POP and non-DUA UD criteria. Primary lower urinary tract symptoms (LUTS) such slow stream, straining, hesitancy, urgency and frequency were recorded. The association between DUA and POP stages was assessed. The concomitance of lower urinary tract dysfunctions (LUTD) such as urinary retention was also evaluated.
Ethical standards were performed according to the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained before enrollment in the study. Local Ethics Committee for Clinical Trials (University of Verona) determined that the approval for this investigation was unnecessary since it only involved standard clinical practice. This research was registered in the clinical audit in our hospital.

Statistical analysis

Statistical analysis was performed with IBM-SPSS ver. 17 for Windows (IBM Corp, Armonk, NY). Continuous variables were reported as mean and standard deviation. Categorical variables were expressed as numbers and percentages. Student t-test and the Mann-Whitney U test were performed to compare continuous variables, as appropriate. Categorical variables were tested with the χ^2 test. Statistical significance was set at $p \leq 0.05$.

RESULTS

Data was collected on 330 women, with mean age (years) 63.7 ±18.4, all of whom had anterior vaginal wall defect. A concomitant apical defect (uterine/vaginal vault) requiring surgical correction was diagnosed in 38 women (11.5%). According to any of the 4 UD criteria for DUA, this condition was found in 166 females (50.3%), while normal detrusor contractility in the voiding phase was demonstrated in the remaining 164 women (49.7%). Table 1 reports the stratification of women according to POP-Q stages in the overall group, in the DUA group and in the non-DUA group. In all groups, POP-Q stage 2 was the most represented, while POP-Q stage 4 was the least. Comparison of DUA and non-DUA females

Table 1. *Detrusor underactivity and normal detrusor contractility (No- DUA) incidence in women with pelvic organ prolapse staged by Pelvic Organ Prolapse Quantification system*

	Overall population	DUA women	No- DUA women	p
# of patients	330	50.3% (166/330)	49.7% (164/330)	
POP-Q stage				
2	56.4% (186/330)	45.2% (84/186)	54.8% (102/186)	0.3
3	33.3% (110/330)	50.9% (56/110)	49.1 (54/110)	1
4	10.3% (34/330)	76.5% (26/34)	23.5% (8/34)	0.006

DUA – detrusor underactivity; No- DUA – normal detrusor contractility; POP-Q – Pelvic Organ Prolapse Quantification

Table 2. *Rates of lower urinary tract symptoms in women with pelvic organ prolapse: comparison between patients with detrusor underactivity and control group (no detrusor impairment)*

Symptoms	DUA (n = 166)	Control group (n = 164)	p
Slow stream: n (%)	130 (78.3%)	78/164 (57.3%)	0.1
Straining: n (%)	81 (48.8%)	65 (39.6%)	0.008
Hesitancy: n (%)	69 (41.6%)	56 (34.1%)	0.004
Urgency: n (%)	129 (77.7%)	107 (65.2%)	0.05
Frequency: n (%)	117 (70.5%)	75 (45.7%)	0.08

DUA – detrusor underactivity; n – number of patients

Table 3. *Main urodynamic comparison between patients with detrusor underactivity and control group (no detrusor impairment)*

UD data (median)	DUA (n = 166)	Control group (n = 164)	p
Pdet/Qmax (cmH_2O)	11	20	0.01
Qmax (ml/sec)	10	15	0.01
PVR (ml)	190	20	0.00

UD – underactivity; Pdet/Qmax – detrusor pressure at peak flow; Qmax – peak flow; PVR – post void residual

according to the POP-Q stages showed that in DUA women POP-Q stage 4 was significantly higher. In contrast, POP-Q stage 2 and 3 were not statistically different between females with detrusor underactivity and normocontractility. LUTS were more common in those with DUA, with statistical significance for each symptom except for slow stream (Table 2). In women with POP and DUA, we found low rates of urinary retention: 5.4%. In table 3 are reported the main different urodynamic data between the two groups.

DISCUSSION

We found a higher prevalence of DUA in women undergoing UD for symptomatic POP (>50%) than previously reported [4, 5, 6]. However, data on DUA frequency in this population is poorly comparable due the different UD criteria used. In a recent study on 518 women with POP, DUA rate was reported as 40.9% [4]. However, the author's used a diagnostic parameter validated only for males (Bladder Contractility Index) [14–17]. This questionable choice was likely impacted their outcomes. In another study, using PIP-1 Griffith parameter, the pre-operative DUA prevalence was only 19%, but with a very low sample size (63 women; 6). For these reasons, the evaluation of the actual occurrence of DUA in women with POP is still challenging, and the few data available are not really comparable. In our study, we followed the main internationally recognized UD criteria for female DUA diagnosis in a large cohort [8–12]. The aim of our choice was to reduce bias in identifying women with DUA. Indeed, DUA diagnosis related to UD characteristics that met at least one of these criteria may have improved the accuracy of our findings.

Detrusor impairment in women with POP is likely a consequence of bladder outlet obstruction (BOO). In general, detrusor underactivity may be caused by either neural or muscular factors. The latter may be due to detrusor muscle damage or reduced excitability by neural stimuli. The former is represented by impairments at any level of the neural pathways of control of micturition, which may lead to an inappropriate transmission of contractile stimuli. They comprise impaired synaptic transmission, denervation, nerve damage, and reduced input from the pontine micturition center. Thus, the consequences of POP on detrusor function have to be considered in this perspective.

The main pathophysiological mechanism leading to development of DUA in women with POP is likely traction caused by prolapse which leads to an obstructive kinking and compression of the urethra. This may exert detrimental direct effects on other structures which may contribute to the development of DUA. Increasing postvoid residual may lead to bladder overdistension, and thus add further damage to the detrusor due to muscle tissue ischemia. Behavioral factors or functional alterations of the cerebral centers involved in the control of micturition are conceivable, but evidence is lacking.

BOO provokes numerous compensatory pathophysiological changes of the detrusor muscle tissue, which ultimately compromise efficacy of contraction [18, 19]. Not surprisingly obstruction has also been shown to lead to reduced receptor density and innervation of the detrusor muscle [20, 21, 22]. While the effects of obstruction on detrusor function have been extensively investigated, consequences of direct effects of traction are less clear. Currently available literature only shows a correlation between POP and nerve damage, but a possible relationship between them and DUA has not yet been addressed [23]. Detrusor underactivity may arise from chronic detrusor ischemia, which in turn may be the result of hypertrophy due to BOO [24, 25, 26]. Whether tractional forces in POP may further contribute to bladder ischemia has not been investigated. It is known that for every muscle fiber an optimal stretch length exists, at which the fiber develops its maximum contraction [27]. Assuming that a healthy, non-prolapsed bladder allows the optimal contraction of all its muscular components, it is conceivable, that at least parts of a prolapsed, deformed bladder are not able to develop their maximum contractional force. Interestingly, the rate of detrusor impairment increased dramatically in women with POP-Q stage 4 and DUA was significantly associated with the highest grade of POP. This finding may be explained by the more obstructive effect of high-stage prolapse, and by the prolonged time of bladder outlet obstruction and mechanical traction and ischemia. In POP-Q stage 4, muscle fibers may have lost their contraction strength showing that the exposure over time to a worsening POP-Q stage might create a no turning back bladder condition whereby even

with prolapse reduction the contractile ability will not return. According to this theory it may be advisable to identify patients with POP before their prolapse progresses to POP-Q stage 4. DUA occurred approximately in half of the patients with symptomatic POP-Q stage 2 and 3, and was three-fold higher in females with stage 4. Surprisingly, DUA was approximately equally distributed in the lower POP-Q stages (2 and 3), with a ratio of almost 1:1 between DUA and no-DUA patients. This points to the significant prevalence of DUA in older women with even lower stages of POP. In the subgroup of women with POP-Q stage 4, a detrusor impairment should be highly supposed and preoperative invasive urodynamics may be considered to allow appropriate counselling and avoid patient disappointment in cases of persistent voiding symptoms after surgery [28].

A consequence of detrusor failure can be represented by voiding symptoms. Usually, in women with POP these LUTS are supposed to be related to the obstructive mechanism of the vaginal wall defect. However, the high rate of DUA even in low stages indicates that those voiding symptoms may not be due solely to the obstructive effect of POP, but also to the development of an underlying DUA condition. This latter disorder could partially or completely explain some of the preoperative voiding symptoms of these women and the lack of improvement after surgery that sometimes occurs. Our data showed higher rates of voiding symptoms in women with DUA. This finding confirmed that emptying disorders may be only partially due to POP-related BOO, while in a non-negligible percent of women they may depend on detrusor impairment.

DUA showed a high prevalence in all POP stages, especially in stage 4. Voiding symptoms may be due to chronic bladder outlet obstruction but also to detrusor failure. Hence, in the case of symptomatic POP, preoperative UD may give additional functional data that may be useful to better tailor surgical counselling.

Strengths of our study are the large sample size and the choice of the most commonly used and internationally recognized UD criteria existing for the diagnosis of female DUA to provide robust epidemiological data on this under researched topic.

One limitation of our study was the lack of post-operative urodynamics; nevertheless, this epidemiological study was focused on the assessment of DUA prevalence and relation to the POP stages as its primary endpoint, and not on the POP surgery and outcomes of surgical treatments. A second limitation was the lack of a standardized and worldwide accepted UD parameter for the diagnosis of female DUA, however this is an intrinsic limit related to this topic per se. The control group consisted of women attended our office for symptoms related to POP but not claiming LUTS as a problem. At our analysis they showed some LUTS, although significantly lower than in DUA women. An ideal CG should have included asymptomatic patients for LUTS, but this is very rare in female population with POP. This could be a limitation of our study, but it represents also a picture of real practice.

CONCLUSIONS

DUA is highly prevalent in women with symptomatic anterior prolapse. DUA was diagnosed in approximately half of the women undergoing UD for symptomatic POP, and it was three-fold higher in those with POP-Q stage 4. LUTS were more common in DUA patients, and clinicians should be aware that urinary symptoms in women with POP may also result from the development of detrusor impairment.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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REVIEW PAPER

UROLITHIASIS

Evolving types of pudendal neuromodulation for lower urinary tract dysfunction

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Introduction Sacral neuromodulation and posterior tibial nerve stimulation for lower urinary tract dysfunction (LUTD) and overactive bladder yield good and reliable results. However, neuromodulation research is continuously evolving because there is still need for more patient-friendly treatment options in the therapeutic management of LUTD. Pudendal neuromodulation (PNM) has been emerging as a promising alternative treatment option for the last few decades. The aim of this study is to review the current state of the art of PNM.

Material and methods A wide literature search was conducted in the field of PNM using Medline through the PubMed database and Elsevier using the Scopus database; a critical review of the results was then carried out. PNM has been studied in its various possible aspects: percutaneous PNM, transrectal/transvaginal PNM, and both percutaneous and transcutaneous dorsal genital nerve stimulation.

Results Each technique was found to result in promising improvements in different clinical outcomes, with some trials reporting even better results than sacral neuromodulation.

Conclusions As a result of a comparison between the various PNM techniques with both sacral neuromodulation and posterior tibial nerve stimulation, we think that PNM should be seen as seriously promising, and we believe it will expand the treatment options for overactive bladder. Even though several studies accordingly showed PNM to be safe and effective, a systematic review and meta-analysis were not feasible. PNM in its various techniques is a promising treatment for LUTD. Nevertheless, further research is needed to include it in treatment algorithms.

Key Words: pudendal neuromodulation ‹› lower urinary tract dysfunction ‹› overactive bladder ‹› neuromodulation ‹› sacral neuromodulation ‹› posterior tibial nerve stimulation

INTRODUCTION

Overactive bladder (OAB), defined by the International Continence Society as 'a syndrome characterized by urgency with or without urgency incontinence, usually with frequency and nocturia', affects approximately 16.5% of adults [1]. It affects tens of millions of people worldwide, necessitating an economic burden through treatment costs [2]. Furthermore, lower urinary tract dysfunction (LUTD) has a profound negative impact on the quality of life.

Nevertheless, first-line conservative treatments such as antimuscarinic agent therapy do not always lead to sufficient improvement in symptoms of OAB and are often associated with disabling adverse effects [3] with discontinuation rates nearing 50% in the first month of treatment [4, 5].

Electrical stimulation of the sacral roots, generically described as 'neuromodulation', has emerged as an alternative and attractive treatment for refractory OAB [4]. Research towards neuromodulation for overactive bladder (OAB) has been increasing over the past decades [6].

Sacral neuromodulation (SNM) and posterior tibial nerve stimulation (PTNS) are effective and safe third-line treatments for OAB. Their overall success rates range from 43 to 85% and 40 to 79.5%, respectively [7]. SNM has been used for refractory OAB 'dry' (without urinary incontinence) and 'wet' (with urinary incontinence) for more than 2 decades, with success rates of 70–80%, similar to those of intravesical botulinum toxin [8]. Since the approval of InterStim therapy by European Conformity (CE) (1995) and the Food and Drug Administration (FDA) (1997), SNM has become an established advanced treatment option for OAB, which has treated more than 375,000 patients worldwide [9].

Nevertheless, both SNM and PTNS rarely completely alleviate the initial symptoms. Another limitation is the reoperation rate of 30% to 40% [10] in SNM, while PTNS treatment requires frequent outpatient visits for administration. The future holds great promise for new and improved treatment methods for this pervasive, costly condition. A recent review highlighted that there is still a need for more patient-friendly treatment options for OAB [2021,11]. Therefore, several new neuromodulation modalities have been studied in the last decades, besides the 2 abovementioned, which are the most studied. Many of them yield promising results; however, they are yet to be implemented and have to live up to the current standard of care. It is hypothesized that SNM works by inhibiting the voiding reflex by means of electrical stimulation of sensory afferent fibres. Many of the sensory afferent nerve fibres contained in the sacral plexus transmit signals from the pudendal nerve [12]. The urethra is predominantly innervated by the pudendal nerve, mostly known for its motor control of the external urethral sphincter (EUS) and the sensory control of the perineal area [13]. Therefore, theoretically, it is not surprising that direct stimulation of the pudendal nerve has been reported to be effective for bladder inhibition [12]. We refer to this as pudendal neuromodulation (PNM), and it is the most studied neuromodulation modality after SNM and PTNS.

Only 7% of patients with bothersome urgency urinary incontinence (UUI) were found to be treated with any third-line treatments. Hence, Bretschneider et al. highlighted the need for improved treatment algorithms to escalate patients with persistent symptoms, or to adjust care in those who have been unsuccessfully treated [5].

The purpose of this manuscript is to address the available literature advancements in PNM and to present its current state of the art.

MATERIAL AND METHODS

A literature search was conducted on Medline using the PubMed database and Elsevier using the Scopus database in March 2023. The search strategy was based on the following keywords: 'overactive bladder', 'lower urinary tract dysfunction', 'pudendal nerve stimulation', 'pudendal neuromodulation', 'pudendal nerve', 'dorsal genital nerve stimulation', and 'lower urinary tract dysfunction', and it was conducted according to the PRISMA 2020 guidelines [14]. Articles were included according to inclusion criteria (randomized controlled trials, prospective trials, large retrospective studies) and exclusion criteria (case reports, outcomes not clearly expressed in full text). The references lists of the included studies were also scanned. We limited the search to reviews and studies with accessible full text in the English language. The authors independently assessed all the found articles for possible biases, and a collective decision was made whether to include those deemed at high risk due to missing results or unclear methodology. The included studied were grouped according to treatment modality. The present review was not registered, and no protocol was required. No sources of financial or non-financial support were available or needed for this review. The authors declare they have no competing interest in the review. For any enquiries (e.g. data availability, data extraction details, etc.) please contact the Corresponding Author.

RESULTS

Twenty articles out of 83 were included in the review, which are shown in the following subchapters (16 relative to pudendal neuromodulation and 4 to dorsal genital nerve stimulation).

Clinical studies on pudendal neuromodulation

Since the late 1980s, PNM has been used as a treatment modality for LUTD, including OAB, urgency and stress urinary incontinence (UUI and SUI), and neurogenic LUTD. Ohlsson et al. treated 29 OAB patients with 4 sessions of maximal electrical stimulation of the pudendal nerve, finding a significant increase in functional bladder capacity and a decrease in the frequency of micturition with no severe side effects [15].

Later, in the early 2000s, prolonged PNM was made possible after Bion-r therapy (Advanced Bionics Corp., Valencia, California) was introduced as a new minimally invasive option for effective neuromodulation [16]. The Bion-r is a self-contained, battery-powered, telemetrically programmable, current-con-

trolled mini-stimulator with an integrated electrode. It can be implanted adjacent to the pudendal nerve at Alcock's canal and be used to directly stimulate the adjacent excitable tissue. Bosch, Groen et al. treated 16 refractory OAB-wet women between 2004 and 2005 [16, 17, 18] with PNM administered through the Bion-r device. The number of incontinence episodes and pads used per day as well as the leakage severity index decreased considerably. However, the use of the device was discontinued, and it never reached the market in the USA.

In 2007 [19] and 2014 [4] laparoscopic techniques for direct endopelvic PNM were described, and then in 2018 [21], a laparoscopic technique for combined SNM and PNM. Both techniques were reported as yielding promising results, with the latter stating PNM to have better results than SNM because it improved urinary and faecal incontinence by direct inhibition of the bladder and rectum and by selective contraction of the anal and urethral sphincters without activation of other nerve fibres in the sacral nerve roots. Nevertheless, the major limitations were the requirement of general anaesthesia and the very small number of case reports published.

In its endopelvic portion, the pudendal nerve is difficult and dangerous to reach using percutaneous puncture techniques because it is located deep within the pelvis and in proximity to the sciatic nerve and major pelvic veins [4]. Hence, the extrapelvic portion of the nerve was preferred for most of the subsequent studies, either percutaneously or with a combined percutaneous and endoscopic approach.

Fifteen neurogenic OAB patients successfully received a percutaneous lead placement to the pudendal nerve and obtained clinical improvement with PNM performed by Spinelli et al. The percutaneous implant was feasible when using the tools used for SNM (i.e. Interstim 3023, Medtronic, Minneapolis, USA), with the correct positioning of the electrode being ensured by neurophysiological intraoperative monitoring. According to the authors, chronic PNM offers a therapeutic alternative for patients affected by neurogenic OAB, which are known to respond worse to SNM and antimuscarinic drugs, and it can take place before using alternatives such as botulinum toxin or major surgery such as bladder augmentation. Furthermore, it is reversible, and the lead can be easily removed if the stimulation is not successful [22]. Nevertheless, one of the drawbacks of such technique is the requirement to use oscilloscope recordings to find the nerve.

An important step forward with PNM was achieved in 2005, when it was chosen as a superior lead in 79.2% of 24 patients with voiding dysfunction simultaneously implanted with pudendal and sacral leads by Peters et al. [23] in a randomized, blinded, crossover trial comparing PNM and SNM. Seventeen of the 24 initial patients were also diagnosed with refractory interstitial cystitis and followed up for 6 months [24]. Comparable to immediately after the treatment, PNM was chosen as the better lead in 77% of patients after 6 months. Hence, PNM was claimed to be an alternative approach to treat voiding dysfunction.

Ninety-five refractory SUI women successfully underwent percutaneous PNM placement in 2012 [25], treated by Wang et al. They proved that the lead placement by an experienced surgeon positively influenced the results as compared as the results of leads placed by an unskilled surgeon (study arm conceived as placebo control group) and showed a satisfactory overall efficacy. A study by the same research group, published in 2016, showed that PNM was significantly more effective in treating 21 women with SUI as compared to another 21 women treated with pelvic floor muscle training and transvaginal electrical stimulation (TES) [26].

Similarly, PNM yielded better results when compared to TES alone in treating, respectively, 80 vs. 40 refractory UUI women in 2017 [27] and when compared to anogenital electrical stimulation for 60 neurogenic LUTD patients in 2018 (40 vs. 20 patients, respectively) [28].

In 2018 [29], Lemos et al. attempted to reduce the risk of damaging the deep neurovascular bundles and the ramifications of the internal pudendal vein and artery by changing the needle access. The needling was shifted approximately 1 cm cranially and medially to the ischial tuberosity at a 45° angle towards the median sagittal plane, and they found that they could stimulate the pudendal nerve accurately, concluding that their technique might be useful. However, they stated that their technique requires further exploration in greater samples.

In 2019, Jottard et al. [30] explored the feasibility of the ENTRAMI technique (sacral transforaminal lead placement under full visual control by trans gluteal endoscopic guidance). In their publication they describe promising feasibility results of 8 dissections with the ENTRAMI technique performed on 4 human cadavers, allowing both PNM and SNM. They claimed the transforaminal approach to be superior to the transgluteal or perineal puncture site due to the intrapelvic rather than subcutaneous course of the lead, making it less prone to migration when flexing the hip, and because the pudendal vessels and nerve can be clearly identified, reducing the risk of damaging them during a blind, percutaneous

technique. Published literature on the ENTRAMI technique, however, is very scarce, only reported to having been performed in few living patients (not for voiding dysfunction but for chronic pain), and all published cases were performed by the same experienced surgical team.

Gu et al. [31] tried a novel technique designed to assist the surgeon in placing the lead, achieving the closest position to the pudendal nerve with the lowest possible risk of damaging other organs, under the guidance of a 3D printed model. They successfully treated 16 patients, describing the surgical method as accurate, reversible, efficient, and minimally invasive. However, a major limitation is that MRI of the pudendal nerve is difficult to obtain, different scanning parameters are required, and 8 h of MRI monitoring were required to obtain the scanning parameters needed to perform the procedure.

Despite the encouraging results with PNM, difficulties in lead placement and a high rate of secondary lead migration impedes its clinical implementation. Subsequent attempts to treat LUTD via neuromodulation were done either directly to the pudendal nerve or to its most distal branch, known as the dorsal genital nerve (DGN), which is suspected to modulate the lower urinary tract through post-synaptic or presynaptic inhibition of bladder afferents. [2]

Dorsal genital nerve stimulation

Percutaneous

In 2008 [32], 19 women with UUI were successfully treated with a 7-day home period of percutaneous DGN stimulation (pDGNS). The lead placement was performed under local anaesthesia and was well tolerated by all subjects without the need for fluoroscopy. After a week of stimulation, 76% of subjects had a ≥ 50% reduction in pad weights and 47% of subjects were completely dry. Improvements were also observed in the number of heavy incontinence events (IE) and severity of urgency events.

Similar results were reported by Van Breda et al. [33] in their feasibility study. The authors implanted a percutaneous DGN lead in 7 patients with non-neurogenic OAB, training them to self-administer the stimulation on demand (being a perceived voiding desire, the stimulus inducing the subject to activate the electrical stimulation) to inhibit an involuntary detrusor contraction. The results indicated that subject-controlled, on-demand pDGNS is possible over a longer period, in a home setting, with a positive effect on non-neurogenic OAB symptoms with UUI. Although the placement is an easy procedure, it is difficult to fixate the electrode to keep it in the correct position. Improvements in hardware, such as a better fixated electrode and an easy-to-control stimulator, were deemed necessary to make on-demand DGN stimulation a clinically applicable treatment possibility.

Transcutaneous

Fjorback et al. [34] showed that undesired detrusor contractions can be suppressed by using an event-driven transcutaneous DGNS (tDGNS) in 8 patients with multiple sclerosis. The event leading to the activation of tDGNS was set as a detrusor pressure above 10 cmH2O.The bladder capacity increased, and the number of incontinence episodes decreased. On-demand, intermittent, and continuous tDGNS may be safe and practical to manage neurogenic detrusor overactivity following spinal cord injury, as demonstrated by Doherty et al., who found that tDGNS increased the time between the first detrusor contraction and the first desire to void, giving the patient enough time to reach the toilet and preventing UUI episodes with no severe side effects [35].

DISCUSSION

At the time of a robust review by Bartley et al. in 2013 [36], PNM was concluded to be an effective treatment of OAB, with success rates of up to 90%, and it was deemed an alternative treatment of OAB, with success rates of up to 90%, and an alternative option for patients refractory to SNM. A review from Kannan et al. found that PNM gives promising results as compared to sham stimulation in treating post prostatectomy UUI (2018 [37]); however, this evidence was of moderate GRADE quality. Some reports indicate PNM to be superior to SNM in treating refractory OAB. Almost all who failed SNM responded to PNM (93.2%). Overall, a positive PNM response was achieved in 71% of participants who underwent PNM for refractory interstitial cystitis and/or OAB [38]. In another study, after temporary stimulation of the pudendal nerve or sacral roots, most of the patients preferred PNM to SNM [10]. According to Marinkovic's personal experience with PNM for OAB, it is a welcome addition for failed-SNM patients, where a 78% success rate was achieved in 26 patients after 5-year follow up. This highlighted the need for PNM to be prospectively studied, with approval sought for its implementation when tertiary treatment fails and a potential secondary OAB treatment when second-line medical treatment fails [2].

The results of the present review show that there are several promising PNM techniques that have been

investigated, some of which have the potential to expand the neuromodulation options for OAB.

The currently clinically available and most used neuromodulation techniques, SNM and PTNS, have several limitations. The main obstacle of SNM is the requirement of general anaesthesia, and for PTNS it is frequent hospital visits for its administration. They both require regular control visits to monitor and adjust the stimulation settings.

The advantages of course do not come without drawbacks: the low quality of literature evidence and the small size of study populations in the described techniques pose as a limitation to the therapeutic field that PNM could cover. The reviewed articles widely vary in terms of outcomes, study designs, length of follow-up, and overall methodological quality, making a meta-analysis of results not feasible.

Nevertheless, we believe that the results should be interpreted as seriously promising, although we recognize a major limitation in the lack of quality of evidence of the reviewed articles, as well as the narrative rather than systematic nature of the present review. The lack of solid bases is counterbalanced by promising clinical results, notably in those cases where previous standard-of-care treatments have failed. An important result comes from the head-to-head, blinded, crossover comparison between SNM and PNM, resulting in a vast patient preference towards PNM. These results could reasonably make PNM an interesting, cutting-edge treatment option for OAB patients. The main advantages of PNM, when comparing the results to those of SNM, are superior clinical results, good tolerance by patients, and ease of performing treatment in an ambulatory or even a home setting.

Contrary to SNM, most of the described PNM techniques are performed under local anaesthesia and can be performed in day-care, and most of them even during an outpatient clinic visit. This contributes towards the aforementioned need for more patient-friendly treatment options for OAB [11].

Should PNM gain more evidence of safety and efficacy and grow in popularity among urologists, its position within the treatment algorithm of OAB would remain to be defined. Considering that only a fraction of OAB patients will be treated with any third-line treatments [5], we believe that the treatment algorithms to escalate patients with persistent OAB symptoms could include PNM in the future. This could be before the escalation to the current third-line treatment or as an addition for patients who did not respond to sacral neuromodulation, as suggested by Marinkovic [2].

A possible reason for the claimed superiority of PNM over SNM is that the pudendal afferent nerves play a key role in inhibiting the voiding reflex. While sacral neurostimulation excites a select few pudendal afferent nerves, direct neurostimulation of the pudendal nerve itself may be superior in suppressing this voiding reflex [2].

Despite all the recognized limitations of the available literature, bearing in mind the results of PNM together with its pros and cons, a head-to-head comparison between it and the currently available neuromodulation techniques could reasonably lead to PNM proving to be less invasive but efficacious where the other treatment options often fail. Indeed, PNM was chosen over SNM in most patients and with less impact on daily activities for both the patient and the urologist – as compared to PTNS – with fewer office visits needed for PNM (although a head-to-head comparison to answer this interesting question has not been carried out).

CONCLUSIONS

The stimulation of the pudendal and dorsal genital nerves to modulate lower urinary tract symptoms is a promising treatment modality. The current techniques that do so have shown to be feasible, safe, and efficacious. However, evidence is limited, and only small samples have been compared. Consequently, neither the EAU nor the AUA guidelines recommend use of PNM. No PNM devices have received approval by any local regulatory agency such as the FDA or EMA (European Medicines Agency). This review highlights the promising results of PNM for the treatment of OAB which is encountered daily by urologists and can be very bothersome for patients. Further efforts are to be done on this topic, preferably using a larger population and possibly by prospectively randomizing patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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REVIEW PAPER

UROLITHIASIS

Extracorporeal shock wave lithotripsy, ureterolithotripsy, and percutaneous nephrolithotripsy challenges in managing spinal cord neuropathy patients. Lessons learned from a scoping review

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Introduction We aim to review the outcomes of shock wave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotripsy (PCNL) for renal and ureteral stones in spinal cord neuropathy patients (SNP).

Material and methods A literature search was performed on 8th March 2023 using PubMed, EMBASE, and Google Scholar with no date limit. Preclinical/animal studies, reviews, letters to the editor, case reports, and meeting abstracts were excluded. Only English papers were accepted.

Results Thirty-five articles were accepted. Five studies focused on SWL, 17 on PCNL, and 6 on ureteroscopy. The remaining articles employed more than one procedure. Stone composition has shifted from struvite to the more common calcium phosphate. SWL showed a very poor stone-free rate (SFR) likely due to challenges in patient positioning, stone visualization, localization, and inability to pass fragments spontaneously. Flexible ureteroscopy and PCNL were associated with a high incidence of infectious complications, long hospital stays, high blood transfusion rate, and intensive care admissions. There were also cases of death. Both procedures were challenging due to genitourinary reconstruction, scoliosis and kyphosis, rib-cage deformity, lower limb contractures, and severe comorbidity which also affected anesthesia. SFR was lower than in non-neurological patients.

Conclusions SWL, ureterolithotripsy, and PCNL should be considered challenging procedures in SNP due to positioning issues, an increased risk of intra and peri-operative morbidity, and even mortality. Computed tomography should be recommended to assess residual fragments as it becomes imperative to minimize a re-intervention in SNP who should be preferably treated in referral centers.

Key Words: kidney calculi ‹› ureteral calculi ‹› ureterolithotripsy ‹› percutaneous nephrolithotripsy ‹› extracorporeal shock wave lithotripsy ‹› spinal neuropathy

INTRODUCTION

The incidence of nephrolithiasis has increased worldwide in the last twenty years with a prevalence ranging from 1–5% in Asia, 7–13% in North America, and 5–9% in Europe [1]. Spinal cord neuropathy patients [SNP) have a greater risk of nephrolithiasis due to multiple factors that increase the likelihood

of developing urinary stones such as recurrent urinary tract infections, chronic indwelling/intermittent bladder catheterization, immobility with subsequent bone resorption and hypercalciuria, lower levels of urinary citrate, urinary stasis, and vesicoureteral reflux [2]. Despite improvements in the management of neurogenic bladder, 7% of spinal cord injury patients develop their first kidney stone within 10 years after injury with a peak of incidence in the first 6 months after trauma [3]. Yet, the recurrence rate is also high in these patients with a reported rate of 34% within 5 years of the first stone episode [4].

Current indications for the management of kidney stones in SNP are the same as in non-neurological patients. Depending on stone burden and location, extracorporeal shockwave lithotripsy (SWL) or flexible ureteroscopy are indicated in kidney stones up to 2 cm, whereas percutaneous nephrolithotripsy (PCNL) is preferred for larger stones [5]. An important consideration in SNP is the need for general anesthesia as spinal anesthesia is difficult when associated with a spinal deformity or for the risk of inadvertently introducing spinal cord infection [5]. A mid-stream urine specimen should always be sent for culture and preoperative infections must be treated [5]. However, mid-stream urine culture is a poor predictor of postoperative sepsis, and a pelvic urine culture or, even better, a stone culture should be collected to predict the actual pathogen in case of postoperative sepsis [6] considering that SNP are at high risk of postoperative infections.

The present study aimed to perform a scoping review on the outcomes of SWL, ureteroscopy, and PCNL for ureteral and renal stones in patients with spinal neuropathy.

MATERIAL AND METHODS

Literature search

A literature search was performed on 8th March 2023 using PubMed, EMBASE, and Google Scholar with no date limit. The following term and Boolean operators were used: (kidney stones OR renal stones OR ureteral stones) AND (neurogenic bladder OR paraplegia OR spinal cord injury) AND (shock wave lithotripsy OR SWL OR retrograde intrarenal surgery OR RIRS OR ureteroscopy OR percutaneous nephrolithotripsy OR percutaneous nephrolithotomy OR PCNL)

Selection criteria

The PICOS (Patient, Intervention, Comparison, Outcome, Study type) model was used to frame and answer the clinical question: P: patients with spinal cord neuropathy and kidney/ureteral stones; I: SWL; ureterolithotripsy; PCNL. C: none; O: complications and stone-free rate (SFR); stone composition. S: retrospective, prospective, and randomized.

Study Screening and Selection

Studies were accepted based on PICOS eligibility criteria. Preclinical and animal studies were excluded. Reviews, letters to the editor, case reports, and meeting abstracts were also excluded. Only English-language articles were accepted. Retrospective studies, prospective studies and prospective randomized studies were accepted.

All retrieved studies were screened by two independent authors through Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Discrepancies were solved by a third author through discussion. The full text of the screened papers was selected if found pertinent to the aim of this review.

RESULTS

Literature screening

The literature search retrieved 316 papers. A total of 68 duplicates were automatically excluded. Then, 248 papers were screened against title and abstract and 195 papers were further excluded because they were irrelevant to the purpose of the present review. The remaining 53 full-text papers were screened for appropriateness and 18 papers were excluded. Finally, 35 papers were accepted and included [4, 7–40]. Figure 1 shows the flow diagram of the literature search.

Study characteristics

All studies were retrospective. There were 5 studies focusing on SWL alone [14, 15, 38–40], 17 on PCNL alone [10, 12, 13, 16, 19–22, 24, 25, 27–33] and 6 on ureteroscopy alone [8, 11, 17, 18, 26, 37]. The remaining studies concerned more than one procedure. Six studies compared SNP to non-neurological patients [23, 26, 27, 30–32]. There was one pediatric study [26]. Tables 1 and 2 show characteristics of the included studies.

DISCUSSION

Stone composition

In the past, most kidney stones in SNP were infection-related, namely struvite stones, with urea-split-

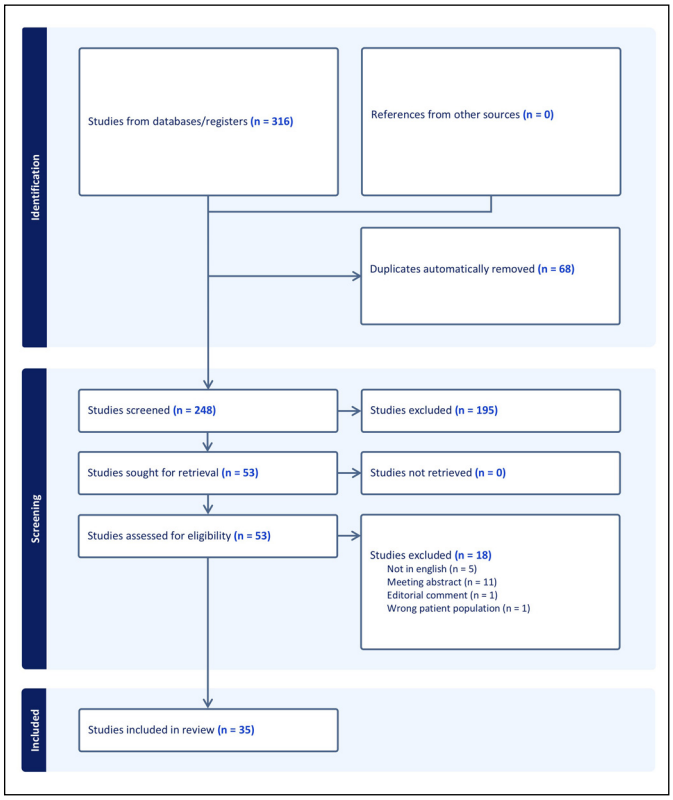

Figure 1. *Flow diagram of the literature search.*

ting organisms such as Proteus mirabilis, Klebsiella species, and Pseudomonas aeruginosa as the main pathogens [2]. More recently, stone composition has shifted from struvite to the more common calcium phosphate as recent literature demonstrated. Clifton et al. [21] and Ganesan et al. [34] found calcium phosphate stones in 82.5% of paraplegic and quadriplegic patients and 42% of patients with multiple sclerosis, a rate much higher than in control groups (15%). This change may be attributed to the improvement of bladder management techniques, such as urological rehabilitation and the use of intermittent catheterization instead of chronic indwelling catheters which lead to a high percentage of infection stones [31]. Ileal-conduit diversion and intermittent catheterization are associated with less bacteriuria, especially from urea-splitting pathogens [36]. Even though struvite stones are still found in a great proportion of SNP, the most prominent crystal identified in this population is calcium phosphate. This can be explained by the increased level of serum calcium and phosphorus in the first several months following an injury during the immobilization period by the mechanism of resorptive bone disease which increase the risk of developing osteoporosis and a low bone mass [41]. The same mechanism contributes to increasing urinary pH (between 5.6 and 7) which is a well-known factor of active stone formation [31]. Compared with matched controls, SNP are less likely to have calcium oxalate monohydrate and dihydrate, calcium carbonate, uric acid, or cystine stones [21, 34].

Outcomes of shock wave lithotripsy

SWL was for many years the cornerstone treatment of kidney stones up to 2 cm in the largest diameter. Though remaining an option in current guidelines, the use of SWL has decreased both in the general population [42] and SNP as demonstrated by the presence of only 5 papers focusing on SWL, all dating back to the 80s and 90s. Wahle et al. treated 31 paraplegic and quadriplegic patients with a total of 54 treatments performed on 42 kidneys, with an average of 2,193 shocks per session [40]. Almost half of the patients required more than one session: 8 patients needed two treatments, 3 patients required three treatments and 3 more patients had four treatments. Postoperative fever >38.5°C occurred in 22% of the 54 sessions. Three months after SWL, SFR was 25.8% but 79% of the stones were reduced by more than 70%.

Lazare et al. performed SWL in 41 renal units in 32 spinal cord injury male patients with a mean stone burden of 2.9 cm [15]. The authors found a good SFR of 78% after a single session but ancillary procedures, including insertion of nephrostomy tubes or double-J ureteral stents, were required before SWL in 66% of cases. Yet, they pointed out that partial staghorn stones required a staged fashion treatment (i.e. 3-4 sessions) with 2,400 shock waves per renal unit per session. Therefore, the authors argued that SWL was effective for the treatment of unbranched and partial staghorn stones only.

In another small series, Niedrach et al. performed SWL in 11 SNP with a total of 19 treatments in 13 renal units [14]. The average number of shock waves per renal unit was 2,350 with a mean power setting of 20 Kv. The main difficulty found by the authors was the shadow of gas and stool from the bowel which made it challenging to target the stone. This was demonstrated by the fact that 3 months after treatment no patient was stone-free and ancillary procedures post-lithotripsy were required in 10 renal units. Complications were mild and there were no symptoms of autonomic dysreflexia episodes.

Robert et al. performed 63 SWL sessions on 23 kidney/proximal ureteral stones in 15 spinal cord injury patients [39]. They demonstrated that SWL was safe with no episode of autonomic dysreflexia and

Table 1. *Characteristics of included studies*

Authors	Stone size	Staghorn stones: Partial/ Full	Definition of stone-free status	Ancillary procedures for residual fragments	Stone-free rate (%)	Recurrence rate (%)	Intraoperative complications N°, (%)	Mean/median length of stay in neurological patients, days	Mean/median length of stay in non-neurological patients, days	Factors affecting complications	Complications in neurological patients	Complications in non-neurological patients
Alsinnawiet et al., 2013	Mean 940 mm^3 (range 360–1,200)	Not reported	Degree of stone clearance was determined by X-ray	SWL or second-look PCNL	60%	80%	Bleeding and Hypotension 1, (25%)	Not reported	/	Not reported	Fever (100%)	/
Baldea et al., 2017	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	LOS, mean (SD) 14.2 days (22.1)	LOS, mean (SD) 9.6 days (12.5)	Spinal cord injury	Pneumonia 96 (5.1%) Sepsis 143 (7.6%) Mortality 80 (4.2%) Myocardial infarction 21 (1.1%)	Pneumonia 50 (2.7%) Sepsis 61 (3.2%) Mortality 59 (3.1%) Myocardial infarction 22 (1.2%)
Beraud et al., 2022	Not reported	Not reported	Not reported	Not reported	Not reported	Neurological group 11.6% (12 months) 15.3% (18 months) 18.3% (24 months)	Not reported	SM (3.0 ±5.6 days) SD (4.3 ±6.7 days) P (4.4 ±11.2 days) T (3.8 ±9.1 days) Overall (3.4 ±7.1)	1.2 (± 2.9)	Not reported	UTI (<10 days following procedures) SM (15,34%), Spinal dysraphism (23.98%), Paraplegia (19.56%) Tetraplegia (20.70%) Neurological (17.70%)	UTI (<10 days following procedures) (3.14%)
Chaudhry et al., 2017	PCNL 2.6 cm (IQR 1.5–2.9) CLL 2.8 cm (IQR 2.2–4.3)	Not reported	Not reported	PCNL	PCNL 60% CLL 71%	Not reported	PCNL group Bleeding 1, (4.3%)	PCNL LOS 4.4 days (IQR 3.5–4.6) CLL LOS 1,4 days (IQR 1.2–1.9)	/	Cobb-S angle >60 degrees	SIRS in 4 patients after PCNL	/
Chen et al., 2002	Not reported	Not reported	Not reported	Not reported	83%	34% (5 y)	Not reported	Not reported	/	Not reported	Not reported	/
Christman et al., 2013	Median NGB 6 mm (4–8) Control group 7 mm (5–10)	Not reported	No stones on renal/ bladder TC or US or URS	/	63% NGB 86.6% Control	45% NGB 14.5% Control	/	Not reported	Not reported	/	Bacteriuria 67% Pain with stone episode 24%	Bacteriuria 16.4% Pain with stone episode 84.7%

Table 1. *Continued*

Authors	Stone size	Staghorn stones: Partial/ Full	Definition of stone-free status	Ancillary procedures for residual fragments	Stone-free rate (%)	Recurrence rate (%)	Intraoperative complications N°, (%)	Mean/median length of stay in neurological patients, days	Mean/median length of stay in non-neurological patients, days	Factors affecting complications	Complications in neurological patients	Complications in non-neurological patients
Clifton et al., 2014	Not reported	Not reported	No evidence of residual or recurrent nephrolithiasis on CT, urogram, nephrostogram and US	13, PCN 7, URS 4, SWL	47.4%	19.0%	Not reported	Not reported	/	Hypercalciuria secondary to immobilization, chronic infection and indwelling catheters	/	/
Culkin et al., 1986	Not reported	7 (2/5)	Renal tomograms followed by nephrostogram	PCNL	90.4%	65.2%	RA (3.6%) Hydrothorax (3.6%), Perirenal abscess (7.2%)	Not reported	Not reported	Atelectasis, Infected decubiti	Bacteriuria 100%, Indwelling Foley catheters 60.9%, Fever 64.3%, Dislodged nephrostomy 21.4%, Anemia 27.8%	/
Culkin et al., 1990	Not reported	SCI 13 (8/5) Control Group 6 (4 /2)	Renal tomograms followed by nephrostogram	PCNL	88.6% SCI 98.5% Control 94% Overall	Not reported	Perirenal abscesses, RA, pneumonia, nephrocolonic fistula, hydrothorax. 1 mortality for CID	Not reported	Not reported	Respiratory problems, complex stone disease	Perirenal abscess (8.8%) Aspiration pneumonia (2.8%) Hydrothorax (2.8%; Nephrocolonic fistula 2.8%; Respiratory arrest 2.8% Hemorrhage (48.6%); fever (74.2%) Dislodged nephrostomy tube (17.1%) Retained stones (11.4%)	Nephrodudenal fistula (1.4%) Hemorrhage (20%); Fever (12.3%) Dislodged nephrostomy tube (4.6%) Retained stones (1.5%) Ureteral edema (6.1%)
Eswara et al., 2013	Median Same day PCNL 15 (range 7–40 mm) Delayed PCNL 18 (range 5–36 mm)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Same-day PCNL: LOS 4 days (range 2–50) Delayed PCNL: LOS 3 days (range 2–14)	/	Urinary stasis, Recurrent UTI, Indwelling catheters, RVU	/	/
Ganesan et al., 2017	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	/	Not reported	Not reported	/

Table 1. *Continued*

Authors	Stone size	Staghorn stones: Partial/ Full	Definition of stone-free status	Ancillary procedures for residual fragments	Stone-free rate (%)	Recurrence rate (%)	Intraoperative complications N°, (%)	Mean/median length of stay in neurological patients, days	Mean/median length of stay in non-neurological patients, days	Factors affecting complications	Complications in neurological patients	Complications in non-neurological patients
Gnessin et al., 2011	Not reported	Not reported	Not reported	PCNL second look	Not reported	Not reported	Not reported	/	/	Infected urine, Vesicoureteral reflux, catheterization, neurogenic bladder	/	/
Irwin et al., 1991	Mean stone burden SB 3.4 cm SCI 1.9 cm	8	Not reported	SWL	OPEN 71% PCNL 70%	OPEN 0% PCNL 20%	Not reported	OPEN: Mean LOS 22 days (8–60) PCNL: Mean LOS 7 days (5–14)	/	Stone burden Skeletal deformities	Fever 16 (100%) Hemorrhage 1 (6.2%) pain 4 (25%) Wound infection 2 (12.5%) UTI 3 (18.85%) Pressure sores 2 (12.5%)	/
Knox et al., 2012	Mean 3.31 cm	Not reported	No evidence of stone on imaging (RX, TC IVU) after procedure	7, PCNL 4, SWL 1, URS	Initial stone--free rate 60.6% Final stone free rate 69.7%	Not reported	Not reported	Mean LOS 5.3 days 9 patients needed ICU-care and mean LOS was 13.9 days	/	Multiple access and increasing stone	Fever 12 (25.5%) Sepsis 8 (17%) Pyelonephritis 1 (2.1%) Acute respiratory distress syndrome 2 (4.2%) Bleeding/Transfusion 4 ((,4%) Arteriovenous fistula 1 (2.1%) Amputation extremity 1 (2.1%) Pressure wound (1 2.1%) Death 1 (2.1%) Acute renal failure 2 (4.2%) Hemothorax 1 (2.1%)	/
Lawrentschuk et al., 2005	Mean stone area 480 (70–3500) mm^2	24	Stone fragments >2 mm	2 monitored 2 SWL 2 URS 1 pyelolithotomy	87%	Not reported	Not reported	Not reported	/	Not reported	Fever 58% Blood transfusion 12% Calyceal perforation 8% Pneumothorax 8% Urosepsis 4%	/

Table 1. *Continued*

Authors	Stone size	Staghorn stones: Partial/ Full	Definition of stone-free status	Ancillary procedures for residual fragments	Stone-free rate (%)	Recurrence rate (%)	Intraoperative complications N°, (%)	Mean/median length of stay in neurological patients, days	Mean/median length of stay in non-neurological patients, days	Factors affecting complications	Complications in neurological patients	Complications in non-neurological patients
Lazare et al., 1988	Mean stone burden was 2.9 cm (range 0.2 to 8.0 cm.)	7 (2/5)	Free of stones or without any radiographic evidence of calcification overlying the collecting system	2 nephrostomy 1 PCNL 1 cystolithotomy	73%	Not reported	Not reported	Not reported	/	No Double J or nephrostomy insert before SWL	Sepsis 1 (3%)	/
Matlaga et al., 2006	Not reported	Not reported	No evidence of calculi by CT imaging in first postoperative day	Not reported	30%	Not reported	Not reported	Mean LOS 3.3 days (range 2 to 10)	/	Not reported	Fever 6, (18.75%) Pressure sore 1 (3.1%)	/
Mitchell et al., 2018	Not reported	43	No evidence of calculi in postoperative imaging. (unenhanced CT, US, and/or intravenous urogram)	Not reported	46% SB 82% non-SB	23% SB 0% non-SB	SB 6, (23.5%) 2 anesthetic, 3 bleeding, 1 renal pelvic perforation; 2 difficult access non-SB 2 (4.9%) bleeding	Median (IQR) hospital stay 7 days (6 to 8)	Median (IQR) hospital stay 4 days (3 to 5)	Mobilization was a problem for pressure sores; increased prevalence of matrix stone is a problem for sepsis; Risk of bleeding was much higher in SB for difficult percutaneous access.	Sepsis 38% Transfusion 11.8%	Sepsis 1.6%, Transfusion 1.6%
Morhardt et al., 2018	Mean stone burden 15.7 mm ±11.2	Not reported	CT, ultrasound, and plain radiography	Second and third look URS	17%	Not reported	0%	Mean LOS days ±SD (range) 3.1 ±1.9 (Range 1-8)	/	Primarily urinary tract infections	Primarily urinary tract infections 19 (15%), Sepsis requiring intensive care unit 2 (2%)	/
Nabbout et al., 2012	Average 31.3 mm (exclude staghorn)	8 (30.8%)	Complete absence of stones or presence of insignificant fragments (<2 mm) at CT scan one day after procedure	Second and third look PCNL	PCNL 53.8% 2nd PCNL 80.8% 3rd PCNL 88.5%	Not reported	Bleeding 6 (28.6%)	Not reported	/	Limited pulmonary capacity and prolonged immobilization, making the anesthetic requirements more complicated	Urosepsis 3 (4.3%) Transfusion 6 (28.6%) Pneumothorax 1 (4.7%) Perforation 1 (4.7%)	/

Table 1. *Continued*

Authors	Stone size	Staghorn stones: Partial/ Full	Definition of stone-free status	Ancillary procedures for residual fragments	Stone-free rate (%)	Recurrence rate (%)	Intraoperative complications N°, (%)	Mean/median length of stay in neurological patients, days	Mean/median length of stay in non-neurological patients, days	Factors affecting complications	Complications in neurological patients	Complications in non-neurological patients
Niedrach et al., 1991	Average of the length of each stone 33.4 mm	0	No visible stone at plain--abdominal x-ray	Not reported	44%	Not reported	Not reported	Average LOS 3.3 days (1–8)	/	Not reported	hypertension1, (9%) hypotension1 (9%) bradycardia 1 (9%)	/
Prattley et al., 2019	Mean stone length, mm 26.7 ±14.5 [5–59]	0	Residual fragments were less than 2 mm at XRKUB, US or CTKUB	Second look URS	47%	42%	Not reported	Median LOS 1 days (range, 0–9)	/	Not reported	urinary infections 2 (10%) sepsis 3, (14%) lower respiratory tract infection 2, (10%)	/
Raj et al., 1999	Mean aggregate stone diameter ±SD 22.3 mm ±18.0 (2–77)	Not reported	Absence of stones on postoperative imaging (X-ray or CT)	Not reported	55%	73%	Not reported	Not reported	/	Not reported	Not reported	/
Robert et al., 1995	Mean of maximum dimension 11 mm (range 5–35)	Not reported	Fragment <3 mm at plain abdomen radiograph	URS	53%	14%	Not reported	Not reported	/	Not reported	Few cases of gross hematuria which spontaneously regressed	/
Rubenstein et al., 2004	Not reported	Not reported	Removal of the entire stone burden to visual completion with no fragments seen on follow-up imaging	Second PCNL	96%	Not reported	Hydrothorax 1, (4.3%); Respiratory difficulty 1, (4.3%); Collecting system perforation 1, (4.3%)	Average LOS 7.04 days (range 1 to 22)	/	Atelectasis poor thermoregulatory mechanisms, pyelolymphatic backflow of bacteria	Fever 11, (47.8%) Hydrothorax 1, (4.3%) Hydrothorax 1, (4.3%) Retroperitoneal abscess 1, (4.3%) Ileus 1, (4.3%)	/
Sofimajidpour et al., 2016	Mean of kidney stone size 35.7 ±6.1 mm (25 to 45 mm)	8 0/8	KUB and kidney US first day after surgery, Non-contrast CT 6 months after surgery	Second PCNL	First PCNL, 53.1 % Second PCNL 78.1%	Not reported	Not reported	Mean LOS 8.3 ±3.1 days	/	Not reported	Blood transfusion, 7 (24.1%) Visceral injury, 2 (6.8%) ICU stay, 7 (24.1%) Urosepsis, 6 (20.6%) Fever 11 (38%)	/

Table 1. *Continued*

Authors	Stone size	Staghorn stones: Partial/ Full	Definition of stone-free status	Ancillary procedures for residual fragments	Stone-free rate (%)	Recurrence rate (%)	Intraoperative complications N°, (%)	Mean/median length of stay in neurological patients, days	Mean/median length of stay in non-neurological patients, days	Factors affecting complications	Complications in neurological patients	Complications in non-neurological patients
Spirnak et al., 1988	Not reported	1 0/1	Not reported	Not reported	60%	Not reported	Hypertension	LOS ranged from 5 to 43 days (mean 17 days)	/	Not reported	Not reported	/
Stauffer et al., 2017	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Febrile UTI 9%	Febrile UTI 1.4%
Symons et al., 2006	Stone size ranged from 10 to 60 mm; without staghorn the mean stone size was et al, 26 mm	13 0/3	Not reported	PCNL SWL URS	48.7%	Not reported	Not reported	Not reported	/	Difficult airways, abnormal anatomy increasing the risk of pneumo-thorax and a reduction in respiratory capacity	Death 2 (6.9%) major com-plications 5, (17.2%) minor com-plications 8 (27.5%)	/
Tepeler et al., 2015	Mean stone size was 15.9 ±8.6 (6–40) mm	Not reported	Residual stone fragments <3	1	66.6 %	5	None	Mean LOS 2.0 ±2.4 (0–10) days	/	Not reported	Fever 6 (22.2 %) Hypotension 1 (3.7%) UTI 1 (3.7%) Urosepsis 1 (3.7%) Respiratory failure 2 (7.4%)	/
Torricelli et al., 2021	Not reported	Not reported	Absence of any fragments on postope-rative day 1 at CT scan.	Second look PCNL, FURS or SWL	48.70%	Not reported	None	Mean LOS 5.8 ±4.7 days	Mean LOS 3.1 ±1.7 days	Infection, Hypotension Bleeding	Clavien 1 = 1 (2.6%) Clavien 2 = 8 (20.5%) Clavien 3 = 0 (0%) Blood transfu-sion: 5.1%	Clavien 1 = 0 (0%) Clavien 2 = 3 (3.9%) Clavien 3 = 3 (3.9%) Blood transfu-sion: 1.3%
Wahle et al., 1988	Not reported	22	Not reported	5 SWL 4 nephro-stomy tube placement (1 steinstras-se requiring URS)	25% 42% (had between 90 and 99% reduction in stone surface area).	Not reported	None	Average of 4.2 days, (IQR 2–14)	/	Not reported	1 nephrectomy five months after SWL. 1 patient with a proximal right ureteral stone underwent ure-terolithotomy	/

Table 1. *Continued*

Authors	Stone size	Staghorn stones: Partial/ Full	Definition of stone-free status	Ancillary procedures for residual fragments	Stone-free rate (%)	Recurrence rate (%)	Intraoperative complications N°, (%)	Mean/median length of stay in neurological patients, days	Mean/median length of stay in non-neurological patients, days	Factors affecting complications	Complications in neurological patients	Complications in non-neurological patients
Welk et al., 2013	Not reported	Not reported	Not reported	Multiple PCNL	Not reported	Not reported	None	Median of LOS 5 days (IQR 3–8).	/	Not reported	The 30-day mortality rates after any stone--related procedure was low. Subsequent ICU admission was required in 12% of cases; none occurred after SWL. ACUTE KIDNEY INJURY with the need for dialysis was rare	/
Wolfe et al., 2013	Stone size <1 cm: 32.8%; 1.0–2.0 cm: 35.8%; >2 cm: 31.3%	Not reported	Removal of any stone larger than 4 mm	URS 31% SWL 16% PCNL 15%	34.40%	71.60%	Ureteral perforation (1.5%)	Not reported	/	Chronic obstructed pulmonary disease	Urosepsis (17.9% Respiratory failure (4.5%) Acute outlet obstruction (4.5%)	/
Wong et al., 2023	Not reported	Not reported	Not reported	URS; SWL; PCNL	Not reported	Not reported	Not reported	Not reported	/	Not reported	Not reported	/

CT – computed tomography; URS – ureteroscopy; SWL – extracorporeal shock wave lithotripsy; PCNL – percutaneous nephrolithotomy; LOS – length of stay; CLL – cystolitholapaxy; SIRS – systemic inflammatory response syndrome; MS – Multiple sclerosis; UTI – urinary tract infection; IQR – interquartile range; NGB – neurogenic bladder; ICU – intensive care unit; SD – standard deviation; FURS – ; KUB – kidney ureter bladder; US – ultrasound; IQR – interquartile range

Table 2. *Type of patients and procedures, aim and outcomes of included studies*

Author	Number of patients	Type of spinal neuropathy and number of patients	Comparison Group	Procedure	Pre-stented patients or with a nephrostomy tube	Antibiotics prophylaxis	Aim of the study	Conclusion
Alsinnawiet et al., 2013	5	SB, 5	/	PCNLs	20% (stent)	Broad-spectrum antibiotics	To present our experience in patients with SB and severe spinal abnormality undergoing PCNL for large stone burden.	PCNL in patients with SB is challenging but safe. Second-look PCNL and additional SWL/URS treatment may be required to completely clear stones.
Baldea et al., 2017	39868	SCI, 1,918	37950	PCNL	Not reported	Not reported	To evaluate outcomes of SCI patients undergoing PCNL in a large patient population and compared outcomes.	PCNL in SCI patients is associated with an increased complication rate and longer hospital stay.
Beraud et al., 2022	45,745,055	MS, 116,730 SD 5,503 P 19,181 T 10,436	45,593,205	SWL, rURS, fURS, PCNL, Open or Laparoscopic surgery	Not reported	Not reported	To compare the incidence and the safety outcomes associated with ASRP (active stone removal procedure) between neurological and non-neurological patients.	The results confirm and clarify the incidence and the safety outcomes associated with ASRP within the neurological population.
Chaudhry et al., 2017	23	SB, 23	/	15, PCNL 17, CLL	Not reported	Treatment based on pre-operative urine cultures	To determine whether stone-free rates after PCNL or CLL were associated with anatomical factors. Secondary outcomes included assessing whether SFR were associated with operative time, estimated blood loss and perioperative complications following PCNL and PC.	The SFR after a single procedure is modest. The severity of scoliosis and kyphosis may be predictive of a more challenging stone surgery.
Chen et al., 2002	77	SCI, 77	/	60, Conservative 7, SWL 14, PCNa 4, SWL and PCN 1, Litholapaxy	Not reported	Not reported	To document the recurrence rate of kidney stones in patients with SCI and to assess the potential contributing factors and long-term renal function outcome.	Despite advances in urologic treatment of persons with SCI, the recurrence rate of kidney stones is still substantial. The causality of stone formation is multifactorial.
Christman et al., 2013	147	PNB, 20	127	147, URS	Not reported	Perioperative antibiotics against surgical related infection	To evaluate if URS in patients with neurogenic bladder would be associated with an increased risk of complications and a lower stone clearance rate than in patients without neurological impairment.	Patients with NGB have significantly increased morbidity related to URS with a predominance of infection related complications.
Clifton et al., 2014	95	13, CP 11, MS 15, SB 56, SCI	/	40, PCNL 28, URS 26, SWL 1, Nephrec-tomy	Not reported	Not reported	Identify changes in stone composition and surgical outcomes in patients with para and quadriplegia.	Para and quadriplegic patients with urolithiasis can be difficult to treat surgically with prolonged hospitalizations, low stone-free status, and often require additional procedures.
Culkin et al., 1986	23	18 quadriplegics 5 paraplegics	/	PCNL	Not reported	Perioperative antibiotic determined form urine culture.	To evaluate the success rate of stone removal and the incidence of operative complication.	PCNL is more effective and results in less morbidity than open lithotomy A repeat PCNL is safer and more effective in total stone excision than open lithotomy.

Table 2. *Continued*

Author	Number of patients	Type of spinal neuropathy and number of patients	Comparison Group	Procedure	Pre-stented patients or with a nephrostomy tube	Antibiotics prophylaxis	Aim of the study	Conclusion
Culkin et al., 1990	100	27 quadriplegics 8 paraplegics	65	PCNL	Not reported	Systemic antibiotics by preoperative urine culture for 48 hours preoperatively and continued post-operatively until the patient was afebrile for 48 hours.	To evaluate the success of complete stone excision, operative morbidity and mortality were compared in two patient population: SCI patients and ambulatory patients.	SCI patients are at higher risk than the non-SCI patients for significant complications with PNL but still have a high overall success rate.
Eswara et al., 2013	246	16 MS 10 SB 4 quadriplegia 3 Paraplegia 2 CP	/	PCNL	14% (stent)	Patients with positive urine cultures were treated with targeted antibiotics for 4–7 days prior to the surgery. The others received oral antibiotics for 4–7 days based on the most recent urine culture sensibility. In PCNL: intravenous levofloxacin or gentamicin at the time of percutaneous access	To determine whether a delayed PCNL reduces the rate of bacteremia/ sepsis in patients with neuromuscular disorders.	Delayed PCNL results in lower rates of bacteremia and/or sepsis in patients with neuromuscular disorders.
Ganesan et al., 2017	587	MS	/	PCNL, SWL, URS	Not reported	Not reported	To compare stone composition in patients with multiple sclerosis (MS) against patients without MS.	Patients with MS have a high incidence of calcium phosphate stones and struvite stones.
Gnessin et al., 2011	367	11 SCI 7 MMC 2 MS 2 CP 1 DM	334	PCNL	Not reported	One week of tailored antibiotic therapy before undergoing PCNL for at least 1 week before surgery.	To assess the composition of renal calculi and metabolic characteristics in a cohort of patients with MS who underwent PCNL.	Although patients with MS anomalies are traditionally thought to harbor infection-related calculi, most have calculi of metabolic etiology.
Irwin et al., 1991	16	11, SB 5, SCI	/	Open, PNL, SWL	Not reported	Parenteral antibiotics pre-operatively and after surgery.	To evaluate the management of renal stones in the spinal patient.	PCNL is the preferred initial treatment of renal stones in spinal patients leaving SWL to treat residual fragments. Open surgery will be reserved for patients in whom PCNL fails.

Table 2. *Continued*

Author	Number of patients	Type of spinal neuropathy and number of patients	Comparison Group	Procedure	Pre-stented patients or with a nephrostomy tube	Antibiotics prophylaxis	Aim of the study	Conclusion
Knox et al., 2012	47	16, SB 26, SCI 2, MS 1, SLA 1, sacral agenesia 1, Triad syndrome	/	PCNL 30 Fr sheath 26 Fr rigid nephroscope	Not reported	Antibiotics were instituted 1 week before procedure based on urine culture.	To evaluate predictors for increased length of stay, intensive care unit stay, stone-free rate and number of procedure between SCI and SB patients undergoing PCNL.	Increasing stone size and multiple access were predictors of adverse outcome. Location of access affected stone free status. No differences in outcome between SB and SCI patients.
Lawrent-schuk et al., 2005	26	26 SCI	/	PCNL 28 Fr sheath	Not reported	Antibiotics 24 h before surgery until 48 h after procedure	To present our experience of PCNL for treating urolithiasis in patients with SCI using a single-stage dilatator for percutaneous access.	PCNL has high success rate and acceptable complication rate compared to SWL and remains a valid first line treatment opinion for kidney stone in patients with SCI.
Lazare et al., 1988	32	18, cervical SCI 9, thoracic, SCI 5, lumbar SCI	/	SWL	66% (both stent and nephrostomy)	Antibiotics according to urine culture, discontinued 1 week after SWL	To evaluate the efficacy of SWL in the treatment of SCI patients with large stone burdens.	SWL is effective for the treatment of unbranched and partial staghorn calculi in the spinal cord injury. SWL alone is less effective for the treatment of full staghorn calculi.
Matlaga et al., 2006	32	14, SCI 18, MMC	/	PNL 30 Fr sheath Rigid and flex nephroscope	Not reported	2 weeks of tailored antibiotic therapy before undergoing PNL.	To defined the composition of renal calculi in a contemporary cohort of patients with neurogenic bladder who underwent PNL.	Many patients with NB due to SCI or MMC undergoing PNL will be found to have calculi that are metabolically derived rather than calculi secondary to chronic infection with urea-splitting organisms.
Mitchell et al., 2018	53	13, SB	50	PCNL	Not reported	Not reported	To evaluate peri- and postoperative outcome of PCNL in patients with SB undergoing PCNL with historically matched controls.	PCNL in patient with SB is associated with multiple parameters of poor outcome and should be counseled about increased perioperative risk and likelihood of recurrence
Morhardt et al., 2018	46	46, SCI (due to traumatic, vascular, or malignant mechanisms)	/	Ureteroscopy flexible and rigid	16% (stent)	Positive urine cultures: 1 week preoperatively tailored therapy continued throughout surgery. Negative urine culture: standard perioperative prophylactic antibiotics.	To evaluate the association of clinical factors on outcomes in patients with SCI undergoing ureteroscopy.	Ureteroscopy is a safe and effective method for treating kidney stones in patients with SCI. Patients with higher levels of SCI had lower SFRs and may warrant special consideration to limit complications.

Table 2. *Continued*

Author	Number of patients	Type of spinal neuropathy and number of patients	Comparison Group	Procedure	Pre-stented patients or with a nephrostomy tube	Antibiotics prophylaxis	Aim of the study	Conclusion
Nabbout et al., 2012	21	14 SCI 7 SB	/	PCNL	Not reported	Treated with a culture specific oral antibiotic for at least 1 week before the procedure. Broad spectrum antibiotics were administered intravenously at admission	To evaluate the managing stones with PCNL in patients with spinal neuropathy.	PCNL in patients with spinal neuropathy had a stone clearance rate comparable with that of the general population. These patients, however, needed multiple PCNLs to be stone-free and had a higher incidence of complications (especially infectious).
Niedrach et al., 1991	11	5, congenital abnormalities 4, Trauma 2, MS	/	SWL	27.3% (stent) 54.5% (nephrostomy tube)	Treatment based on pre-operative urine cultures. Antibiotics including aminoglycosides, third-generations cephalosporins, for yeast infection amphotericin B. If patient remained afebrile for first postoperative night, the antibiotics were switched to oral dosing	To determine the effectiveness of SWL in patients with spinal cord impairment.	Fragmentation rate in patients with spinal cord dysfunction was excellent, the clearance of stones was poor and delayed.
Prattley et al., 2019	21	15, cervical SCI 6, thoracic SCI	/	URS (flexible and rigid)	27% (stent)	Single dose gentamicin (3 mg/kg) at induction unless pre-operative urine cultures dictated otherwise.	To evaluate the experience at a regional SCI unit for ureteroscopy in upper tract stone disease in patients with SCI.	Ureteroscopy provides a useful treatment option for patients with SCI, but SFR are inferior to those in the general population.
Raj et al, 1999	20	20, Neural tube defects, (tumor, trauma and infarcts were excluded)	/	SWL; PCNL; URS; open	Not reported	Not reported	To identify the incidence of nephrolithiasis documented by radiography and elucidate risk factors that may have contributed to stone formation.	Risk factors for stone formation were analyzed and bacteriuria was invariably present. Vesicoureteral reflow, pelvicalicectasis, renal scarring and a thoracic level spinal defect were also associated with an increased risk of stone formation.

Table 2. *Continued*

Author	Number of patients	Type of spinal neuropathy and number of patients	Comparison Group	Procedure	Pre-stented patients or with a nephrostomy tube	Antibiotics prophylaxis	Aim of the study	Conclusion
Robert et al., 1995	15	12 secondary to closed trauma 2 secondary to a bullet injury 1 iatrogenic	/	SWL	Not reported	Parenteral antibiotics immediately before SWL and for 1 week when preoperative urine cultures were positive.	To evaluate the efficacy of SWL in paraplegic and tetraplegic patients.	SWL is effective in spinal cord injury patients, but its particular usefulness and limitations in this patient population need to be kept in mind. Once fragmentation of the calculi is achieved, elimination from the urinary tract remains a problem.
Rubenstein et al, 2004	23	23, SB, SCI, exstrophy/epispadias, neonatal meningitis, stroke, and spine chondrosarcoma	/	PCNL	100% (nephrostomy 24 hour prior to PCNL as routine care)	Culture-specific oral antimicrobial agents 48 hours before admission if they had a history of urinary tract infection or colonization and were admitted the night before the access procedure for administration of broad-spectrum intravenous antimicrobial agents	To reviewed our experience performing percutaneous nephrolithotomy (PNL) on patients with neurogenic bladder dysfunction with special attention paid to the risks of surgical complications and stone recurrence.	PNL in patients with neurogenic voiding dysfunction is safe and effective, with outcomes comparable to that of patients without such lesions.
Sofimajidpour et al, 2016	29	24, SCI 5, SB	/	PCNL	Not reported	Not reported	To investigate technical problems, complications and stone clearance rate in patients with spinal neuropathy undergoing PCNL.	Although patients with spinal cord injury have problems in terms of surgery and complications, percutaneous nephrolithotomy is an appropriate and safe treatment method for kidney stones.
Spirnak et al., 1988	5	5, Cervical SCI	/	SWL	Not reported	Intravenous antibiotics 48 h before the procedure based on culture and sensitivity results	To report results of SWL kidney stone treatment in traumatic quadriplegic patients.	SWL may be performed safely in quadriplegic patients without the added morbidity of a general or spinal anesthetic.

Table 2. *Continued*

Author	Number of patients	Type of spinal neuropathy and number of patients	Comparison Group	Procedure	Pre-stented patients or with a nephrostomy tube	Antibiotics prophylaxis	Aim of the study	Conclusion
Stauffer et al., 2017	402	34, SCI	368	URS	13.6% (nephrostomy tube) 40.1% (stent)	In patients with prior infections treated with ureteral stenting or nephrostomy tube placement, a full 2-week course of antibiotic therapy was administered before ureteroscopy. In cases of a positive preoperative culture, targeted antibiotic treatment was initiated within a minimum of 3 days before the procedure.	To characterize the rate of febrile UTI after ureteroscopy in patients with neurogenic bladder compared with those with physiologically normal bladders.	Although infectious complications in the neurogenic population are likely multifactorial, the reliance on catheterization and thus colonization appears to be a significant factor and extends to non-neurogenic patients. Bacterial colonization may be the significant underlying risk factor for febrile UTI after ureteroscopy.
Symons et al., 2006	29	9, SCI 10, SB 10, other causes	/	PCNL, SWL	27.6% (nephrostomy tube) 17.2% (stent)	Urine cultures were obtained in all patients preoperatively and appropriate antibiotic prophylaxis was used prior to the procedure. All patients received antibiotics postoperatively for 48 h	To assess the technical difficulties, associated complications and stone clearance rates in patients with spinal neuropathy undergoing percutaneous nephrolithotomy.	Technical difficulties and potential complications should be considered carefully before undertaking percutaneous nephrolithotomy in these patients.
Tepeler et al., 2015	19	6, quadriplegics 13, paraplegics	/	URS, RIRS	Not reported	Not reported	To evaluate the outcomes of fURS in patients with SCI.	fURS is an effective procedure for UTU stone in patients with spinal cord injury.

Table 2. *Continued*

Author	Number of patients	Type of spinal neuropathy and number of patients	Comparison Group	Procedure	Pre-stented patients or with a nephrostomy tube	Antibiotics prophylaxis	Aim of the study	Conclusion
Torricelli et al., 2021	117	39, SCI	/	PCNL	Not reported	Patients with positive urine culture received antibiotic therapy for 1 week before surgery. Those with negative urine culture received third generation cephalosporin starting 24 h before surgery	To assess the complication and SFR of PCNL in patients with SCI and to evaluate whether this population should be assigned a GSS of 4.	Patients with SCI should not be automatically assigned GSS 4. SFR is related to stone burden in these patients, but they have a higher complication rate and a longer hospital stay than non-neurological patients.
Wahle et al., 1988	31	8, quadriplegic 23, paraplegic	/	SWL	12.1% (nephrostomy tube)	Not reported	To assess the efficacy and safety of SWL as a treatment modality for renal stones in paraplegic and quadriplegic patients.	In paralyzed patients, SWL plays an important role in the treatment of stones less than 3 cm.
Welk et al., 2013	5,121	66	/	URS; ureteral stent/ percutaneous nephrostomy; SWL, PCNL	Not reported	Not reported	To describe the incidence, management and outcomes of surgically treated kidney stones after SCI and to evaluate the impact of a past history of kidney stones on the occurrence of kidney stones.	During intermediate follow-up after SCI, surgically treated upper tract kidney stones occur in 1.3% of patients. URS is the most common treatment. A history of surgically managed kidney stones before SCI portends a higher risk of stones after SCI.
Wolfe et al., 2013	67	SCI, 29	/	URS	Not reported	Broad spectrum antibiotics for 48h post operatively	To review the outcomes and safety of URS for the treatment of urolithiasis in the SCI population.	URS in the SCI population is an effective treatment for ureteral or renal stones but may be associated with greater risks and reduced efficacy.
Wong et al., 2023	189 .739		/	SWL, URS	Not reported	Not reported	To determine risk factors and time course for repeat procedures after URS or SWL procedure using a large employer-based claims database.	Patients with paralysis and neurogenic bladder had a significantly higher risk of repeat stone procedure. SWL was associated with higher risk of repeat procedure than URS.

ABL – acute blood loss; AD – autonomic dysreflexia; ASRP – active stone removal procedure; CLL – cystolitholapaxy; CP – cerebral palsy; CT – computed tomography; fURS – flexible ureteroscopy; GA – general anesthesia; LOS – length of stay; MD – muscular dystrophy; MMC – myelomeningocele; MS – multiple sclerosis; NGB – neurogenic bladder; P – paraplegia; PCNL – percutaneous nephrolithotomy; PNB – pediatric neurogenic bladder; rURS – rigid ureteroscopy; SB – spina bifida; SCI – spinal cord injury; SD – spinal dysraphism; SFR – stone-free rates; SIRS – systemic inflammatory syndrome; SWL – extracorporeal shock wave lithotripsy; T – tetraplegia; UTI – urinary tract infections

a few cases of gross hematuria occurred which however ceased spontaneously. Auxiliary procedures were performed in two cases to remove ureteral stone fragments with a Dormia basket. SFR was 53%. Conversely, Spirnak et al. had 2 cases of significant intraoperative hypertension in traumatic quadriplegic patients with no anesthesia, despite no case of complete clinical syndrome of autonomic dysreflexia occurred [38]. Therefore, it is recommended that such patients should be carefully monitored throughout the treatment.

In summary, we found that SWL in this subset population has a very poor outcome likely due to challenges in patient positioning, stone visualization, localization, inability to pass fragments spontaneously, and need for anesthesia to prevent neuropathic events.

Outcome of ureteroscopy

Semirigid and flexible ureteroscopy for ureteral and kidney stones have shown a good safety profile and clearance rate in the general population. Ureteroscopy may be associated with more complications in SNP who are at higher risk of postoperative infectious complications. This was confirmed by Stauffer et al. who demonstrated that febrile urinary tract infections following ureteroscopy were significantly higher in patients with neurogenic bladder compared with control patients (9% vs 1.4%, p = 0.01) with higher rates in those dependent on bladder catheterization (12.5% vs 1.4%, p = 0.003) [18].

Christman et al. compared ureteroscopy outcomes for upper urinary tract stones of 20 pediatric patients with a neurogenic bladder with 127 controls [26]. The neurological group had 22 stone episodes, requiring a total of 45 ureteroscopy procedures, while the control group had 138 stones episodes with a total of 173 procedures required. Interestingly, non-neurogenic patients had a significantly higher percentage of pain associated with the stone episode (84.7%) than bladder-neurogenic children (24%). Conversely, the latter presented with a greater percentage of associated bacteriuria compared with controls (67% vs 16.4%, respectively). Surgical time was significantly longer in neurogenic patients. Similarly, complications were more common in neurological patients (25% vs 16.6%) than in controls, including one death. Specifically, infectious complications were again more frequent in the neurological population (23% vs 5.8%) with a lower SFR (63% vs 83.6%).

Ureteroscopy in SNP can be challenging not only for infectious complications but also for anatomical variation such as lower limb contractures, access via Mitrofanoff or suprapubic tracts, and increased comorbidity [37]. Prattley et al. performed flexible ureteroscopy for ureteral and kidney stones in 21 spinal cord injury patients for a total of 41 procedures [37]. A ureteral access sheath was used in 63% of cases. Seven patients required a repeat ureteroscopy as a multistage approach due to the level of stones. Postoperative outcomes were satisfactory with a median postoperative stay of one day (range, 0–9 days). Complications were acceptable with 3 cases of sepsis, 2 cases of lower respiratory tract infections, and one case of autonomic dysreflexia. Despite the use of baskets for active fragments removal, SFR was low at 47%. At a median follow-up of 46 months, stone recurrence occurred in 42% of patients. Ensuring a complete stone clearance, i.e. zero fragments, is essential in patients with a high level of spinal neuropathy since immobility makes the passage of residual stone fragments less likely. This partly explains the higher risk of stone recurrence in such patients.

Tepeler et al. had similar results in a series of 19 patients with upper ureteral and kidney stones [17]. There were 3 major complications (1 sepsis and 2 respiratory failure) that required admission to the intensive care unit. Single-stage SFR was 57.1% and after additional ureteroscopy sessions, 66.6% of the 21 renal units were finally stone-free.

The challenge of ureteroscopy in this population was also confirmed by Wolfe et al. in a cohort of 29 male patients who required an average of 2.3 ipsilateral ureteroscopies because stone clearance of any stone >4 mm after the first procedure was only 34.3% [8]. Interestingly, 45.5% of patients with residual fragments were secondary to technical or procedural limitations due to failure to identify or insert the ureteroscope through the ureteral orifice (45%) and inability to successfully access all of the stones (40%).

Some factors have been identified to be associated with worse SFR. Morhardt et al. showed that patients with no preservation of sensory or motor function in the sacral segments S4-S5 [OR 0.16, 95% CI 0.03–0.82) and an average of 2.2 procedures per patient were associated with lower odds of stone-free status (OR 0.83, 95% CI 0.03–0.32) [11].

Our review cautions urologists who perform flexible ureteroscopy in these patients that apart from infectious complications, they must be adequately prepared for genitourinary anatomical challenges, often superimposed with lower limb contractures, modifying access approaches through reconstructed lower tracts and, at times, even supported by percutaneous approach. All of the aforementioned factors increase the level of challenge and morbidity of a minimally invasive approach.

Outcomes of percutaneous nephrolithotomy

PCNL has become widely accepted as the preferred approach for managing large kidney stones, even in patients with anatomical anomalies of the kidney, severe obesity, spinal diseases, and prior renal surgery. However, most SNP present with immobilization, altered body habitus, severe scoliosis and kyphosis, rib-cage deformity, and often with reconstructed urinary tracts already from childhood. All the aforementioned factors could play a relevant role in performing PCNL. Prone PCNL could cause restrictive lung disease and ventilation difficulties and this problem is at least partly overcome by supine PCNL which should be preferred in such a patient [43]. Cautions must be paid in scoliotic patients who should be placed in an appropriate atraumatic position. Indeed, the short distance between the rib cage and the iliac crest, the curvature of the spine, the pelvic tilt, and the lower limbs contracture may all make positioning and access rather challenging due to a small window for percutaneous access in the prone position [19, 44]. An interesting study by Chaudhry et al. demonstrated the association between increasing anatomic complexity and lower SFR in patients with scoliosis and kyphosis [24]. Anatomic complexity was assessed using the Cobb angle which is the measurement between two lines drawn perpendicular to the superior and inferior vertebral endplates of the curved spine segment. The authors found that patients with worsening scoliosis (median Cobb angle of 43°) had a lower SFR compared with those having a lower median Cobb angle (24°, p = 0.058) [24]. Alsinnawi et al. [20] suggested paying particular attention to patient positioning in case of spina bifida to maintain a safe anesthetic, safeguard pressure points and maximize percutaneous access. The authors suggested using malleable supports, in particular below the curved part of the spine, and adhesive strapping to maintain position and facilitate exposure of percutaneous access. Despite these measures, they found that the range of movement of the nephroscope was inadequate, in particular, in accessing upper calyces [20]. The challenge of PCNL in SNP is additionally demonstrated by the low rate of single-stage stone-free status as demonstrated by several studies. Nabbout et al. performed PCNL in 26 renal units in 21 patients and found that SFR was low at only 53.8% after the first PCNL [25]. This result was in line with studies by Sofimajidpour et al. [12], Symons et al. [34], and Mitchell et al. [19] whereby the SFR of a single-stage procedure was 53.1%, 62%, and 50%, respectively. These studies found that multiple procedures were required to achieve complete stone-free status in several patients and this was mainly related to the presence of complete staghorn stones in up to 30% of their series.

In a series of 23 patients, Rubenstein et al. found that 6 patients required three or more procedures to clear their staghorn stones [10], highlighting that such patients should be counseled about the necessity of more than one PCNL session to achieve satisfactory stone clearance. This reveals that SNP commonly present with a significant stone burden which makes PCNL in this population more challenging. Also it is important to note that in most cases surgery can last more than two hours [12]. Therefore, urologists should be ready to face these situations with a variety of instruments and lithotripsy devices. The abnormal visceral anatomy that may result from skeletal deformities may be responsible not only for failure to access the kidney in PCNL but also in visceral injury and both such problems have been only partly attenuated by supine PCNL. Indeed, visceral injury [12, 32] pneumothorax, hemothorax, and hydrothorax [10, 16, 25, 28, 29, 32] are well-documented complications not only in historical series.

Compared to non-neurological patients, SNP demonstrated significantly longer hospital stays, infectious complications, and blood transfusion rates. Baldea et al. performed a one-to-one matching based on age, race, gender, presence of major comorbidities, and preoperative urinary infections, and compared 1885 spinal cord injury patients with the same number of non-neurological patients [27]. The former had a significantly longer length of stay (mean 14.2 ±22.1 vs. 9.6 ±12.5 days, p <0.001). The authors also found that spinal cord injury status independently increases patient's adjusted odds of both minor and major complications and mortality.

In another comparative study, Torricelli et al. demonstrated that surgical time was significantly longer in spinal cord injury patients (119.41 ±45.58 minutes) compared to controls (141.00 ±45.23, p = 0.018) [30]. Again, the former had a significantly longer postoperative stay (mean 5.8 ±4.7 vs. 3.1 ±1.7 days, p = 0.002). In a historical series back in the 1990s, Culkin et al. compared 35 spinal cord injury patients with 65 ambulatory patients; blood transfusion rate was 48.6% in the former as opposed to 20% in the latter [32]. Despite improved instruments and surgical techniques, more recent series still found a higher rate of transfusion in SNP [19, 30].

Undoubtedly, infections are among the most serious complication following PCNL in SNP. Pneumonia has been reported in many series with a rate ranging from 3% [21, 29, 32, 33] to 5.1% [27]. Spine defor-

mity and spinal neuropathy have also a detrimental effect on lung function due to impairment of respiratory muscles, ineffective cough reduced vital capacity, and reduction in chest wall compliance [45] which could convert into prolonged intubation and acute respiratory distress syndrome [29]. Postoperative fever/urinary tract infections were commonly reported ranging from 10.2% [30] to 25.5% [29], 34% [13], and up to 58% [28]. Perirenal abscess formation was also reported, despite being not common [10, 16, 32]. Sepsis rate with intensive care admission was reported to range from 4% [28], 7.6% [27], 14.3% [25], 17% [29] up to 26% [22]. The risk of postoperative sepsis was found to be twofold higher in SNP compared with non-neurological patients even when controlling for the presence of preoperative urinary infections [27]. The presence of multiple risk factors for infections, such as indwelling catheters, neurogenic bladder, vesicoureteral reflux, and struvite stones, predisposes this population to postoperative sepsis. Delayed PCNL could be an option to reduce the postoperative rate of sepsis. Eswara et al. evaluated 35 patients with neuromuscular disorders and assessed the difference in postoperative bacteremia/sepsis between those who had or had not placed a percutaneous nephrostomy tube at least 24 hours before PCNL [22]. The rate of PCNL bacteremia/sepsis was 14 % but patients undergoing same-day surgery had a 26% rate of bacteremia/sepsis compared to the group who had a preoperative nephrostomy tube which has no cases of it. There were also reported several cases of death [29, 33] with a mortality rate of up to 4.2% [27].

From our review, we infer that PCNL in SNP must be approached with experience and caution. Apart from positioning and anesthesia challenges, these patients are at higher risk of intraoperative complications related to bleeding, organ injuries, need for multiple interventions, poorer SFR and, despite the best precautions, postoperative sepsis and even mortality are a reality. In the bargain for rendering them stone-free, especially if associated with larger stone burdens and infectious stones, a technically challenging surgery can become a life-threatening procedure and this needs to be clearly discussed due to a reverberating impact on the psychosocial profile of patients and caregivers alike.

Summary points

Our review provides a very succinct yet clear message to urologists who manage patients with spinal anomalies/deformities with or without associated neuropathy. The three main challenges include:

A) Anatomical challenges: they may include physical or bony or limb alterations as well as genitourinary reconstructions.
B) Metabolic anomalies: there is an increased risk of stone formation and recurrence with an equal propensity for non-infectious and infectious stones, especially when patients have neurogenic bladders complicated by autonomic dysreflexia when the spinal cord injury is associated with paralysis.
C) Interventional challenges: whether from simple positioning issues or the need for multiple general anesthesia for repeated interventions, there is an increased risk of intra and peri-operative morbidity and even mortality. Urologists should emphasize there is no simple intervention. Any procedure, including SWL, ureteroscopy and PCNL, is far more challenging in this subset of patients and should therefore be preferably carried out in referral centers.
D) SFR assessment: we feel that a low-dose computed tomography scan should be recommended to declare that patient is stone-free as in this subset of patients it becomes imperative to minimize a re-intervention.

Study limitations

We were unable to provide any recommendation from a technical or technological standpoint as rightfully for these patients one treatment does not fit all and hence only a tailored approach may be the best option [46].

CONCLUSIONS

SWL in SNP has a very poor outcome probably due to challenges in patient positioning, stone visualization and localization, and a high rate of residual fragments. Challenges in ureteroscopy and PCNL are linked to frequent difficulties in reaching the stone due to anatomical anomalies, a significantly increased risk of infectious complications, and the need for repeat interventions under general anesthesia. Also these potential problems need to be clearly addressed during counseling. We feel that endoscopic combined intrarenal surgery maybe be a possible best approach for personalized care in these patients and perhaps we need more studies to see if now is the “prime time” for this modality in managing urolithiasis in these patients [47].

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

UROLITHIASIS

Efficacy of combination therapy tadalafil plus tamsulosin in ureteral stents-related symptoms relief

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Introduction Ureteral stents-related symptoms (USRs) are the common complications of ureteral stenting. Tamsulosin a selective alpha-1 blocker and Tadalafil a PDE-5 inhibitor are one of drugs have been used for USRs relief. In this study we aimed to evaluate the effectiveness and safety of combination therapy Tamsulosin+Tadalafil for treating USRs comparing it with the efficacy of either Tamsulosin or Tadalafil monotherapies.

Material and methods 279 patients with indwelled unilateral ureteral stents were randomized to Tamsulosin 0.4 mg + Tadalafil 5 mg once a day (Group 1, n = 67), Tamsulosin 0.4 mg once a day (Group 2, n = 71), Tadalafil 5 mg once a day (Group 3, n = 69) and Placebo once a day (Group 4, n = 72). USRs severity was registered and calculated by using the Ureteral Symptoms Score Questionnaire (USSQ) at the 14th day of treatment. Side-effects and total analgesic use were recorded and compared.

Results At the endpoint in patients with unilateral ureteral stents the combination therapy Tamsulosin + Tadalafil led to statistically lower intensity of urinary symptoms comparing with Tamsulosin (15.2 ±4.3 vs 21.8±3.6, p = 0.0003) or Tadalafil (15.2 ±4.3 vs 20.6 ±2.8, p = 0.0004) monotherapy. All groups of treatment demonstrated significant relief of USRs comparing with Placebo mostly beneficial in the combined therapy group. Body pain and analgesic need in Group 1 was lower than in Groups 2, 3 or 4. Side-effects were registered rarely without statistical differences in frequency between groups.

Conclusions Combination therapy with Tamsulosin + Tadalafil is an effective and safe option that achieves the statistically more significant relief of USRs comparing with Tadalafil or Tamsulosin monotherapies.

Key Words: urolithiasis ‹› ureteral stents-related symptoms ‹› double J ureteral stents ‹› Tamsulosin ‹› Tadalafil ‹› combination therapy

INTRODUCTION

Along with percutaneous nephrostomy, ureteral stenting is the main wide-using method for successful elimination of the upper urinary tract obstruction different etiology [1, 2]. Long-term inserted ureteral stent as a foreign body inside of urinary tract is causing the symptoms of irritation that usually make a negative influence on quality of life in a patient [3]. Ureteral stents-related symptoms (USRs) are the common complications of ureteral stent indwelling and may occur in 80% patients or even more [4]. Tamsulosin, a selective alpha-1 blocker, is the recommended wide-using drug for relief the USRs. Last years, numerous publications informed about the impact of phosphodiesterase-5 (PDE-5) inhibitor Tadalafil, initially designed as erectile dysfunction correction drug, on USRs intensity. The effisacy of Tamsulosin and Tadalafil for elimination of USRs is comparing [5, 6].

Objectives

We aimed to evaluate the effectiveness and safety of combination therapy Tamsulosin + Tadalafil for treating USRs comparing it with the efficacy of either Tamsulosin or Tadalafil monotherapies.

MATERIAL AND METHODS

Between January 2021 to May 2023, 279 patients (178 males and 101 females) aged 38.2 ±19.7 years (range: 18–59 years) with indwelled unilateral Double J (DJ) ureteral stents were randomized to Tamsulosin 0.4 mg once a day + Tadalafil 5 mg once a day (Group 1, n = 67), Tamsulosin 0.4 mg once a day (Group 2, n = 71), Tadalafil 5mg once a day (Group 3, n = 69) and Placebo once a day (Group 4, n = 72). Simple randomization was performed and all investigators (Authors) were blinded.

The exclusion criteria were patients with short-term ureteral stenting (<14 days), fever, congenital urogenital abnormalities, confirmed urological/others oncological diseases, urethral/ureteral strictures, previous diagnosis of overactive bladder, benign prostatic hyperplasia, chronic cystitis, prostatitis and/or chronic pelvic pain, pregnant females, patients with severe liver/renal/heart failure or glaucoma. Patients who had previous stent in the past were not included into the study because of they have commonly different pain/USRs perceptions than naïve patients which is not correct for comparison and may deviate the final results.

Patient's characteristics are presented in Table 1.

All patients were underwent ureteroscopic lithotripsy with indwelling of DJ stent *in situ*. Standard 'Rüsch' DJ ureteral stents size 6 (Ch.) length 26 cm were used in all cases. Medical therapy was prescribed at once after DJ inserting and given for a period of 14–29 days (19.5 ±4.9 days, 95% CI) Patients were recommended to use Sodium Diclofenac for analgesia as *per need*. The Ureteral Stent Symptom Questionnaire (USSQ) developed by Joshi HB et al. in 2003 was the tool that has been used to access USRs severity in patients of each group and filled by every patient at the 14th day of treatment. We analyzed and calculated the survey results thereafter [7]. The safety of the treatment was evaluated as a percentage of side-effects (SEs) among patients included into each group.

Retrograde ejaculation (RE) is a well-known common side-effect of Tamsulosin. Taking into account the emerging health- and sometimes even life-threating conditions which were indications for the indwelling of ureteral stents, we did not consider RE as a significant marker for objective assessment of general health status in the stenting patients therefore we noted, but did not include this issue into the list of SEs in the Group 1 and Group 2 where Tamsulosin was prescribed.

The minimum sample size of study was determined by the clinical Effect Size (ES), variability of the outcome (standard deviation, SD), type I (α) and type II (β) error levels. Primary outcome measure of the study was urinary symptoms (US), clinically significant effect $\Delta = 3$, SD = 4 (ES = ¾ = 0.75). We were interested by the differences of outcomes for the therapies (4 groups) then $\alpha = 0.05/6 = 0.008$ (with the Bonferroni correction for 6 paired comparisons). G*Power v.3.1.9.6 was used for the sample size estimation (Means: Wilcoxon-Mann-Whitney test) [8]. At the Power = 90% minimum sample size is equal to n = 60 per group (n = 240 pts. totally). So, the power of our study was 90% and for this value our sample size was enough (n = 279 pts. totally).

The distribution of parameters was presented by: Mean ± Standard Deviation (M ±SD) for Gaussian distribution or Median (Me) and interquartile range (QI–QIII) for non-Gaussian distribution. The statistical significant difference among 4 groups was determined by ANOVA or Kruskal-Wallis test, correspondingly. For post-hoc comparisons Scheffe's or Dunn's tests, correspondingly, were used. The chi-square test was calculated to compare qualitative data. The level of significance was set at $p < 0.05$. [9]. Analysis was performed using the statistical software EZR v. 1.61 (graphical user interface for R statistical software version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria). Study was approved by the local Ethics Committee. All included patients declared their informed consent in writing.

RESULTS

At the 14th day after ureteral stent placement the combination therapy Tamsulosin + Tadalafil led to statistically lower intensity of urinary symptoms comparing with Tamsulosin (15.2 ±4.3 vs 21.8 ±3.6, p = 0.0003) or Tadalafil (15.2 ±4.3 vs 20.6 ±2.8, p = 0.0004) monotherapy. Body pain in Group 1 was lower than in Groups 2 and 3. Work performance in patients who received combination therapy was higher than in Group 2 (8.3 ±1.4 vs 10.6 ±1.3, p = 0.026) or Group 3 (8.3 ±1.4 vs 11.2 ±1.8, p = 0.018). Improvement in sexual health in groups Tadalafil and Tamsulosin + Tadalafil was similar (3.8 ±1.6 vs 3.5 ±1.3, p = 0.863) and significantly more than 6.7 ±1.4 in Tamsulosin group, p = 0.002 or 8.1 ±1.6 in Placebo group, p = 0.0006 (Table 2, Figure 1). Analgesic need was much lower in Tam-

Table 1. *Characteristics of involved patients*

Characteristic	Group 1 n = 67	Group 2 n = 71	Group 3 n = 69	Group 4 n = 72	p*
Age, yrs	36.5 ±18.3	37.4 ±19.7	38.1 ±17.6	37.2 ±15.2	0.865
M/F ratio	(44/23)	(47/24)	(42/27)	(45/27)	0.899
BMI (kg/m^2)	25.7 ±6.3	24.2 ±5.8	26.1 ±5.2	27.3 ±4.8	0.764
Stented ureter: Left/Right	36/31	32/39	34/35	33/39	0.732
ATS, days	19.6 ±4.2	18.4 ±4.1	20.5 ±6.3	19.8 ±5.4	0.627
Stone Size, cm	1.4 ±0.6	1.6 ±0.5	1.5 ±0.4	1.7 ±0.6	0.783
Comorbidity, n (%)					
Chronic pyelonephritis	18 (26.9)	20 (28.2)	19 (27.5)	22 (30.6)	0.966
Arterial hypertension	13 (19.4)	12 (16.9)	14 (20.3)	16 (22.2)	**0.583**
GERD	17 (25.4)	19 (26.8)	16 (23.2)	17 (23.6)	0.962
Chronic cholecystitis	8 (11.9)	7 (9.8)	6 (8.7)	6 (8.3)	0.892
Arthritis	7 (10.4)	8 (11.3)	5 (7.2)	7 (9.7)	**0.769**
CAD	6 (9.0)	7 (9.9)	9 (13.0)	8 (11.1)	0.880
Diabetes mellitus	5 (7.5)	6 (8.5)	6 (8.7)	4 (5.6)	**0.691**

M/F – male-to-female; BMI – body mass index; ATS – average time of stenting; GERD – gastroesophageal reflux disease; CAD – coronary artery disease; n – number
Group 1 – Tamsulosin+Tadalafil; Group 2 – Tamsulosin; Group 3 – Tadalafil; Group 4 – Placebo; * – chi-square test was used.

Table 2. *Ureteral stent symptom scores according to USSQ domains, side-effects and total analgesic use in examined patients at the 14th day of treatment*

VARIABLES		GROUP 1, Tamsulosin+ Tadalafil, n = 67	GROUP 2, Tamsulosin, n = 71	GROUP 3, Tadalafil, n = 69	GROUP 4, Placebo n = 72	p
USSQ domains	US	15 (14–16) [234]	21 (20–22) [14]	20 (18–21) [14]	36 (34–37) [123]	<0.001*
	BP	6 (5–6) [234]	13 (12–14) [134]	7 (6–8) 12[4]	18 (16–19) [123]	<0.001*
	SM	3 (2–3) [24]	6 (6–7) [13]	3 (2–4) [24]	8 (6–8) [13]	<0.001*
	GH	18 (17–18.75) [4]	18 (17–19) [4]	18 (17–19) [4]	24 (23–25) [123]	<0.001*
	AP	11 (10–12) [4]	11 (10–12) [4]	11 (10–12) [4]	18 (16–19) [123]	<0.001*
	WP	8 (7–8) [234]	10 (9–11) [14]	10 (9–11) [14]	17 (16–18) [123]	<0.001*
TAU		400	1150	600	2100	<0.001*
Side-effects, n (%)		5 (7.5)	4 (5.6)	3 (4.3)	–	0.160**
headaches		2 (3.0)	–	1 (1.4)	–	0.268**
nausea		1 (1.5)	–	1 (1.4)	–	0.548**
facial flushing		1 (1.5)	–	1 (1.4)	–	0.548**
hoarseness		–	1 (1.4)	–	–	0.401**
dizziness		1 (1.5)	1 (1.4)	–	–	0.560**
lightheadedness		–	2 (2.8)	–	–	0.117**

US – urinary symptoms score; BP – body pain score; SM – sexual matters score; GH – General health score; AP – additional problems score; WP – work performance score; TAU – Total analgesic use (Diclofenac, mg); n – number
Notes: median and interquartile range (IQR) are presented.
* – Kruskal-Wallis test was used, Dunn's test was used for post-hoc comparisons:
1 – statistically significance difference from the GROUP 1, p <0.001;
2 – statistically significance difference from the GROUP 2, p <0.001;
3 – statistically significance difference from the GROUP 3, p <0.001;
4 – statistically significance difference from the GROUP 4, p <0.001
** – chi-square test was used

sulosin + Tadalafil group as compared to both Tamsulosin (400 mg vs 1150 mg of Sodium Diclofenac, p = 0.0008) or Tadalafil (400 mg vs 600 mg of Sodium Diclofenac, p = 0.004) groups. In Placebo group the need in analgesia was even more (2100 mg of Sodium Diclofenac). Side-effects were registered rarely and totally occur in 12 (5.8%) patients with following distribution: 5 (7.5%) cases from Group: 1, 4

(5.6%) cases from Group 2 and in 3 (4.3%) cases from Group 3 without statistical differences in frequency (p = 0.160) (Table 2). Box & Wheasker plot for Ureteral stent symptom scores in our patients according to USSQ domains is presented in the Figure 1.

DISCUSSION

Inserting of DJ stents is a routine procedure using for more than 50 yrs that aimed to prevent/eliminate the upper urinary tract obstruction different etiology [10]. USRs are famous complications of ureteral stenting that significantly reduce the quality of life in patients [3]. So, after beginning of ureteral stents using numerous drugs like different analgesics, alpha-blockers and antimuscarinics were proposed to reduce USRs with different degrees of beneficial results [11, 12]. It had been considered that above-mentioned drugs cause ureteric relaxation thereby lead to reducing the pressure transmitted toward the renal cavity during micturition, decrease the top contraction pressure leading to dilatation of ureter and lessen the irritation of bladder with the intravesical part of the stent that caused relief of USRs [13, 14].

Recently have begun to appear the data on the effectiveness of Tadalafil alone and its combination with Tamsulosin on renal calculus clearance after shock wave lithotripsy [15]. Efficacy of tamsulosin versus tadalafil as medical expulsive therapy on stone expulsion in patients with distal ureteral stones is studying [16]. Researchers suggested that Tadalafil can dilate ureters promoting the passage of ureteral calculus.

Farshi Haghro A et al. in 2019 informed that daily use of Tadalafil 10 mg relieves USRs, sexual status and decrease pain comparing with placebo, so it can be used as a new treatment option in the alleviation of lower urinary tract symptoms and can improve the quality of life in patients with DJ stents [17].

According to Balaji AR et al, 2020, Tadalafil can also be used for USRs relief and is as effective as

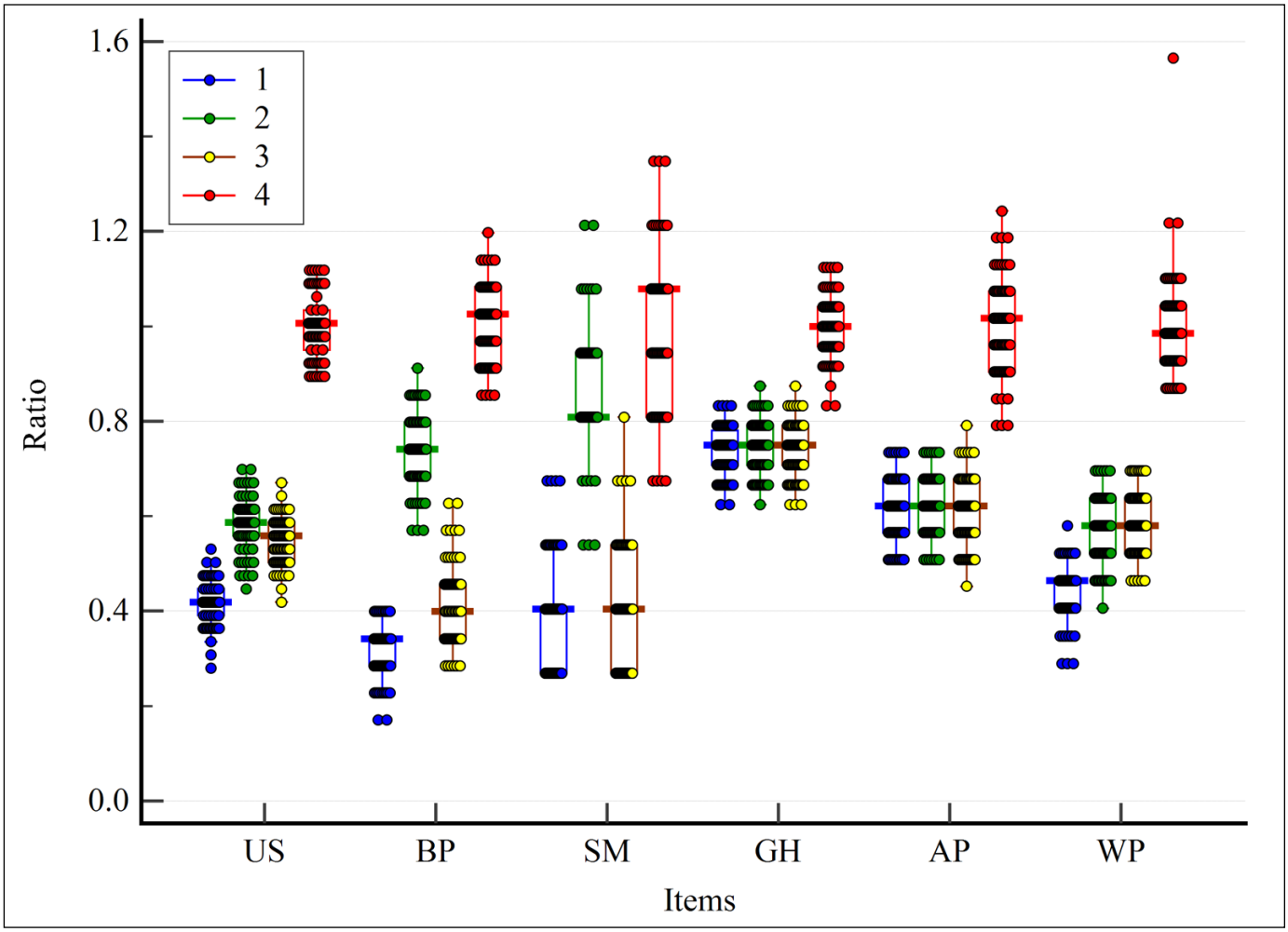

Figure 1. *Box & Wheasker plot for Ureteral stent symptom scores according to USSQ domains in Groups 1–4.*

α-blockers and antimuscarinics in relieving urinary symptoms and is more efficacious in relieving body pain and sexual symptoms [18].

In 2021 Ilyas MRF et al. informed that Tadalafil 10 mg demonstrate significantly better results compared to Tamsulosin 0.4 mg in improving USRs [5]. It is common knowledge that PDE-5 receptors are present in the lower part of ureter, bladder trigone and neck. Because of the PDE-5 receptors are there, Tadalafil a famous PDE-5 inhibitor, reducing spasms and reflux thereby eliminates urinary tract obstruction that can overcome irritation symptoms [19, 20]. Pecoraro A et al. in 2023 summarized that PDE-5 inhibitors are comparable to alpha antagonists, except for a higher improvement of sexual index of the USSQ scores [21]

Bhattar R. et al. informed that Tadalafil and Silodosin relax ureteral smooth muscle that helps in forward propagation of large size ureteroscopes without any high risk of complications or SEs. As for us, one of the main principal and significant results of research was the fact that ureteral orifices were found to be dilated in 69.6% Silodosin group, 60.9% in Tadalafil group, and only 28.6% in placebo group. A large number of patients in groups Silodosin and Tamsulosin had dilated ureteral orifices as compared to the patients in placebo group, whereas difference in visualization of ureteral orifice was statistically insignificant in Silodosin and Tadalafil groups [22]. Presented study clearly demonstrates that Tadalafil has the opportunity to relax the ureter muscles and dilate the ureter as a consequence. This feature can explain the effects of Tadalafil in relief of USRs as well as in promotion of stones passage through the ureter [15, 16].

Our prospective placebo controlled double blinded randomized study demonstrates the efficacy of combination therapy Tamsulosin + Tadalafil for ureteral stents-related symptoms relief comparing with monotherapies by both drugs. We also registered significantly less intensity of USRs in Tadalafil or Tamsulosin monotherapy groups comparing with Placebo. At the 14th day of treatment urinary symptoms in both groups of monotherapy were the same intensity and less than in Placebo group. It should be noted that general health in all groups of treatment was the same and better that in Placebo group (Table 2, Figure 1). Side effects in all three groups of treatment were noted rarely and the same in frequency. Obtained results advocate the expediency of prescribing the effective and safe Tamsulosin + Tadalafil combination therapy for USRs relief in patients with ureteral stents.

We consciously excluded RE from the list of side effects of pharmacotherapy. In our opinion, unlike other unwanted/allergic/somatic *phenomena*, this intimate and only functional parameter does not affect the state of somatic health of patients. That is why RE cannot be considered as a significant SE determining the choice for use any drug in patients with ureteral stents, which a priori must be indwelled to eliminate health/life-threating urinary tract obstruction [23].

We also excluded from the study patients who had previous stenting in the past because of they usually have more intensive pain/USRs perceptions than naïve patients that may deviate total results. In our opinion the additional research of the efficacy combination therapy Tamsulosin + Tadalafil for USRs relief in such repeatedly stented patients is needed.

To our knowledge, this is the first report of the effectiveness of proposed combination Tamsulosin + Tadalafil in ureteral stents-related symptoms relief in patients who underwent ureteral stenting. Presented study has one principal limitation. We investigated the efficacy of intake the dosage 5 mg of Tadalafil only. Considering the presence of 2.5 mg Tadalafil tablets at the pharmacological market, it would be interesting to study the efficacy 2.5 mg, or 7.5 mg in combinations with Tamsulosin 0.4 mg for USRs management. That approach might be promising direction of future investigations.

CONCLUSIONS

Our study shows that combination therapy with Tamsulosin + Tadalafil is an effective and safe option that achieves the statistically more significant relief of ureteral stents-related symptoms comparing with Tadalafil or Tamsulosin monotherapies in patients with inserted ureteral DJ stents. Work performance in examined patients who received combination therapy was higher than in all groups of comparing, while their body pain and analgesic need was much lower.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest. The authors declare no financial support and/or external funding.

ETHICS APPROVAL

Study has received approval from the Institutional Ethic's Committee.

Patients provided written consent for all procedures and study inclusion.

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ORIGINAL PAPER

UROLITHIASIS

The effect of ureteral double J stent insertion on work performance in patients undergoing endoscopic stone treatment

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Introduction Despite the developments in the material of the double J (DJ) stents and the production of thinner ones of desired sizes, patients continue to experience troublesome DJ stent-related symptoms in their lives. This study aimed to determine how DJ stenting affects patients' work performance after endoscopic stone surgery.

Material and methods A total of 107 patients underwent placement of a ureteral stent after ureterorenoscopy (URS)/retrograde intrarenal surgery (RIRS), and only active and full-time working patients were included. All patients were asked to complete the validated Turkish version of the work performance score (WPS) questionnaire in the Ureteral Stent Symptom Questionnaire (USSQ) the day before stent removal and again one month after stent removal.

Results Of the participants, 32.7% (n = 35) were female and 67.3% (n = 72) were male; the mean age was 41 (19–80) years. The workday loss had no statistically significant correlation with patient BMI, stone size, or stent indwelling time (p >0.005); however, a statistically significant negative correlation was detected with patient age (r =-0.335, p <0.001). The medians of WPSs with the stent and without the stent were 6 (3–15) and 3 (3–12), respectively (p <0.001).

Conclusions Although DJ catheterization is a crucial tool for urological practice, it may increase the social and economic burden of patients due to reduced work performance and lost workdays. Therefore, limiting the duration of the DJ stent's stay and providing treatments to minimize patient symptoms will positively impact their professional lives. It would be beneficial to avoid DJ stenting in routine practice unless medically necessary.

Key Words: DJ catheterization ‹› work-performance ‹› stone ‹› endoscopic treatment

INTRODUCTION

When Zimskind et al. introduced the concept of the ureteral stent in 1967, they probably did not expect its use to become so widespread [1]. The Double J (DJ) stent is used in urology practice for many reasons, including surgeries for ureteral-renal stones and to treat ureteral strictures and retroperitoneal pathologies that affect ureters [2]. DJ stents, which are now crucial tools in daily urology practice, have undergone substantial developments, especially when Finney and Hepperlen solved the slip and migration problem of straight ureteral stents by adopting DJ-featured stents in 1978 [3]. However, even with improvements in the material of the stents and the production of thinner ones of desired sizes, patients still experience problems in their daily lives after DJ stent implantation, regardless of the primary pathology [4, 5, 6].

Almost 90% of patients complain of at least one irritative symptom, and some of them experience quality of life problems [4, 5]. The main complaints are increased frequency, urgency, dysuria, flank pain, suprapubic pain, and hematuria due to bladder wall and trigone irritation [4, 5, 7, 8]. Joshi et al. evaluated the ureteral stent-related symptoms by defining and validating the Ureteral Stent Related Symptom Questionnaire (USSQ) in 2003 [9]. The USSQ has been translated into different languages, including Turkish (USSQ-T), and has been widely used in clinical trials to examine patient discomfort [10]. Although some medications, such as α-blockers, antimuscarinics, phosphodiesterase inhibitors (PDEIs), and anti-inflammatory drugs, are used to manage these troublesome symptoms, DJ stent-induced symptoms remain an unpleasant condition for patients [11, 12].

The symptoms caused by the DJ stent do not only affect the personal lives of the patients, but they also affect their professional lives [6]. The loss of workdays and work performance negatively affect the personal and national economic burdens imposed by ureteral stents [13]. In the literature, many studies have reported symptoms after DJ stent placement; however, studies focusing on the effects of the DJ stent on work performance are lacking [11, 14]. The present study aimed to focus on the impact of symptoms caused by DJ stenting on patients' work performance after endoscopic urinary stone surgery.

MATERIAL AND METHODS

This study was approved by the Ankara City Hospital Institutional Review Board (IRB number: E2-23-3309). The data of patients who underwent ureterorenoscopy/retrograde intrarenal surgery (URS/RIRS) for ureteral or kidney stones between 01.06.2022 and 01.01.2023 were retrospectively analyzed. Overall, 107 patients who underwent placement of a ureteral stent (4.8 F, 26 cm standard stent, made of polyurethane) after URS/RIRS were eligible for inclusion in the study. The study group consisted of patients who had active working lives and were working full time. Patients who had missing clinical data, who were younger than 18 years of age, who were students, retired, or part-time workers, or who had a previous ureteral stenting, pregnancy, bilateral ureteral stenting, or obstruction due to malignancy were excluded. Patients' characteristic data (age, gender, body mass index (BMI), and education level), stone size, operation type, lost workdays, stent indwelling time, pain localization (flank, back, suprapubic, or groin/testicular), and work performance scores (WPSs) were recorded. The WPS is a subtitle of the USSQ and includes three questions assessing changes in work quality and performance, changes in work hours due to difficulty in concentrating, and functional limitations in the patient's work life due to urinary symptoms. All patients were asked to complete the validated Turkish version of the WPS questionnaire rated from 3 (very good job performance) to 15 (very poor job performance) in the Ureteral Stent Symptom Questionnaire (USSQ) the day before stent removal and at follow-up one month after stent removal. Pain localization was evaluated as local or multiple sites (2, 3, or 4). The effects of demographic and clinical factors on lost work days and WPS were evaluated by univariate analysis. The WPS evaluated with the ureteral stent in place was compared with the WPS evaluated 1 month after ureteral stent removal (i.e., without the stent).

The Statistical Package for Social Sciences (SPSS), version 22.0 (SPSS, Inc.), was used for statistical analysis. The distribution of the data was tested using the Kolmogorov–Smirnov test. Categorical variables were presented as numbers and percentages. Continuous data were presented as medians (range). The means of parameters that were not normally distributed were compared using the Mann–Whitney U-test and Kruskal-Wallis test. Two different

Table 1. *Demographic, clinical and laboratory results of the patients*

	Mean(range)
Age, year	41 (19–80)
BMI, kg/m^2	28.34 (17.6–37.6)
Indwelling time, day	23 (7–183)
Stone size, mm	8 (5–40)
Lost workday	4 (0–30)
WPS with stent	6 (3–15)
WPS without stent	3 (3–12)
Gender, F/M	35/72
Pain localization	
Flank pain	9 (8.4)
Back pain	19 (17.8)
Suprapubic pain	9 (8.4)
2 sites	23 (21.5)
3 sites	17 (15.9)
4 sites	18 (16.8)
Education level	
illiterate	6 (5.6)
elementary or middle school	42 (39.3)
high school	32 (29.9)
university	27 (25.2)
Operation type	
URS	31 (29)
RIRS	76 (71)

BMI – body mass index; WPS – work performance score; URS – ureterorenoscopy; RIRS – retrograde intrarenal surgery

Table 2. *Comparison of WPS with stent, WPS without stent and workday loss according to demographic and clinical factors of patients*

	Lost workday	p	WPS with stent	p	WPS without stent	p
Gender		0.05		0.8		0.64
Male	4 (0–30)		6 (3–15)		3 (3–12)	
Female	2 (0–20)		6 (3–14)		3 (3–8)	
Education level		0.1		0.97		0.31
illiterate	1 (0–7)		6 (3–8)		3 (3–8)	
elementary or middle school	2.5 (0–20)		6 (3–15)		3 (3–8)	
high school	4.5 (0–20)		6 (3–15)		3 (3–7)	
university	5 (0–30)		6 (3–15)		3 (3–12)	
Operation type		0.97		0.99		0.51
URS	4 (0–30)		6 (3–15)		3 (3–12)	
RIRS	3.5 (0–25)		6 (3–15)		3 (3–8)	
Pain localization		0.22		0.13		0.59
Flank pain	2 (0–10)		4 (3–8)		3 (3–4)	
Back pain	5 (0–20)		7 (3–15)		3 (3–7)	
Suprapubic pain	10 (1–20)		6 (3–10)		3 (3–3)	
2 sites	2 (0–30)		6 (3–13)		3 (3–12)	
3 sites	5 (0–21)		6 (3–15)		3 (3–8)	
4 sites	4.5 (0–15)		7.5 (3–15)		3 (3–6)	

WPS – work performance score

Table 3. *Correlation analysis of patients' demographic and clinical data with WPS with stent, WPS without stent and lost workday*

	Lost workday		WPS with stent		WPS without stent	
	r	p	r	p	r	p
Age, year	-0.335	**<0.001**	-0.155	0.11	0.02	0.84
BMI, kg/m^2	-0.167	0.09	-0.033	0.74	0.193	0.05
Stone size, mm	0.035	0.72	0.004	0.97	0.022	0.83
Indwelling time, day	-0.087	0.37	0.009	0.93	-0.044	0.66

BMI – body mass index; WPS – work performance score

Table 4. *Comparison of WPS with stent and WPS without stent*

	With stent	Without stent	p
WPS	6 (3–15)	3 (3–12)	**<0.001**

WPS – work performance score

lost workday parameters (with and without ureteral stent) were compared using the Wilcoxon test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 107 patients who had stents placed after stone operations were included in the study. The characteristics of the patients are shown in Table 1. Of the participants, 32.7% (n = 35) were female, and 67.3% (n = 72) were male; the mean age was 41 (19–80) years. Cases with DJ stent had an average of 4 (0–30) days of work loss and no days of work were lost after DJ stent removal. Table 2 shows the comparison of the WPS with stent in place, the WPS without the stent (one month after ureteral stent removal), and the lost workdays, according to gender, education level, type of operation, and pain localization. No statistically significant difference was found among these variables ($p > 0.05$). The relationship between workday loss and WPS with patient age, BMI, stone size, and stent indwelling time were examined using Spearman correlation analysis, and the findings are presented in Table 3. Neither the WPS with the stent nor the WPS without the stent showed any statistically significant correlation with patient age, BMI, stone size, or stent stay ($p > 0.05$). Workday loss did not show a statistically significant correlation with patient BMI, stone size, or stent indwelling time ($p > 0.005$); however, a statistically significant negative correlation was detected with patient age ($r = -0.335$, $p < 0.001$).
Table 4 shows the WPSs for patients with and without the stent. The median WPSs with the stent and without the stent were 6 (3–15) and 3 (3–12), respectively ($p < 0.001$).

DISCUSSION

DJ stents are symptomatic in up to 90% of patients, and the symptoms affect the patients' quality of life, thereby imposing social and economic costs [4, 5, 6]. These economic and social burdens have prompted a search for solutions to the complications of catheterization [13]. However, finding a solution requires

an investigation of the reasons for the decreases in work performance among the patients and the resulting increased cost caused by the catheterization, as well as the effects of complications [6, 13]. In our study, we found the mean number of lost workdays was 4 days for the catheterized patients. We also noted that younger patients had a greater tendency toward workday losses, in agreement with the current literature [6, 13]. Leibovici et al. have reported almost 50 % of patients lost a minimum of 2 workdays during the first two weeks after ureteral catheterization due to different pathologies [6]. Another study by Staubli et al. reported that the most substantial reason for economic loss was the loss of workdays associated with work incapacity among younger patients during the patient's catheterization period [4, 13].

Today, studies are frequently carried out on the cost-effectiveness of many treatment methods. When calculating costs in the health field, individual costs are roughly divided into two main groups: direct and indirect costs. The direct costs consist of inpatient treatment, outpatient treatment, and drug costs, whereas the indirect costs include lost workdays, caregiver costs, and other costs [14]. In addition to lost workdays, the importance of the poor performance that patients will experience in their professional lives in the post-operative period cannot be neglected. Patients with DJ stents may experience a decrease in work concentration and functional capacity due to symptoms such as flank pain, dysuria, etc., as well as a decrease in the time spent actively at work during the working day due to urgency and frequent urination. All these reasons can lead to a decrease in the quality and efficiency of the work performed, even if it is not observed as a loss of working days [9]. In our current study, when we compared the WPS scores of the patients in the stented and stent-free periods, we found that the WPS scores were statistically significantly higher in the stented period than in the stent-free period. From this point of view, it can be concluded that DJ stents cause a decrease in work performance as well as a loss of workdays in patients.

We still do not have an ideal stent; therefore, we can only try to reduce the symptoms and shorten the indwelling time [2, 13], and some studies have recommended a few solutions [2, 4, 5, 13]. In their meta-analysis of 490 studies, Tang et al. found no significant difference in post-operative complications between the group that underwent DJ stenting and the group that did not undergo DJ stenting after uncomplicated endoscopic stone surgery. Nonetheless, the group that received DJ stent experienced worse LUTS scores [15]. In a prospective randomized trial, Bach et al. compared DJ stenting with post-operative 6-hour ureteral catheter placement. The results showed a statistically significant loss of seven workdays in the DJ stent group compared to three days in the ureteral catheter group [16]. These findings suggest that avoiding the use of a DJ stent when unnecessary could allow patients to return to work earlier without additional risk of complications. If the patient has been catheterized, assigning an appointment day for removal of the DJ stent when patients are discharged from hospital becomes important to avoid exceeding the set catheterization time and thereby avoiding symptom-induced limitations [13]. Furthermore, informing patients about DJ stents and the symptoms that the stents may cause increases cooperation during the postoperative course [4]. For symptomatic improvements, the use of analgesics, α-blockers, PDEIs, and antimuscarinic drugs or intravesical instillations is recommended in some studies [2, 11, 12, 17]. In recent years, emerging technologies, such as computer-assisted stent tracking methods or the development of softer distal coiled stents, are also being investigated to address stent problems [5].

Our study has some limitations, including its retrospective design and the small number of patients included. Another is that the stone localizations and their intraoperative statuses (impacted, infected, etc.) were not evaluated separately. Third, the occupations of the patients were not assessed according to their daily active working hours and working patterns or whether they held office jobs or jobs that required physical strength. A further limitation was the subjective nature of the questionnaire.

CONCLUSIONS

Although DJ catheterization is a crucial tool for urological practice, it may increase the social and economic burden of patients due to reduced work performance and lost work days. Therefore, limiting the duration of the DJ stent's stay and providing treatments to minimize patient symptoms will positively impact their professional lives. It would be beneficial to avoid DJ stenting in routine practice unless medically necessary.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Central European Journal of Urology

ORIGINAL PAPER

UROLITHIASIS

Assessment of the incidence and risk factors of postoperative urosepsis in patients undergoing ureteroscopic lithotripsy

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Introduction Ureteroscopic lithotripsy (URSL) is an approved, minimally invasive, low-risk procedure for urolithiasis treatment. However, some patients may develop urinary tract infection (UTI) post-procedure, eventually leading to urosepsis. Determining the predictors of infection after URSL would help identify patients at a high risk of urosepsis, thereby enabling the early implementation of effective treatment. Therefore, we aimed to establish the incidence and predictors of urosepsis after URSL.

Material and methods We assessed 231 patients who underwent URSL using a holmium laser. The incidence of urosepsis during the 30-day post-treatment period was analysed, and potential predictors of urosepsis, including patient characteristics and individual clinical factors, were examined.

Results Statistical analysis revealed that 16.88% of patients had a confirmed positive urine culture before the procedure. Post-procedure urosepsis occurred in 4.76% of patients. Univariable analysis revealed that 3 factors were significantly associated with the risk of postoperative urosepsis: double-J stent insertion before URSL, pre-operative positive urine culture, and MDR pathogen found preoperatively. In multivariable analysis, only positive urine culture remained significantly associated with the risk of urosepsis after URSL.

Conclusions Patients with positive urine culture before URSL are at significantly higher risk of urosepsis in the postoperative period. Hence, urine culture should be routinely performed before planned endoscopic urolithiasis treatment.

Key Words: urolithiasis ‹› ureteroscopic lithotripsy ‹› URSL ‹› postoperative complications ‹› urosepsis ‹› urinary tract infection ‹› Ho:YAG laser

INTRODUCTION

Urinary stone disease remains the most common urological problem even though it has been known for centuries. Currently, epidemiology, risk factors, and the mechanisms of stone formation are well-documented. The aetiology includes geographical, climatic, ethnic, dietary, and genetic factors [1]. Additionally, urolithiasis incidence depends on various disorders such as obesity, diabetes mellitus, or hyperparathyroidism [2]. Despite the numerous studies conducted in this field and the vast knowledge of the disease, the incidence of urolithiasis is still significantly increasing globally [3, 4, 5]. According to epidemiological studies, its prevalence in adults ranges from 1 to 20%, which may increase to as much as 25% in developing countries [2, 5, 6].

Stones in the urinary tract might be classified based on their location. According to previous studies, urolithiasis mainly affects the upper urinary tract [7]. The incidence in kidneys and ureters is 75.08% and 13.62%, respectively, whereas 9.56% of stones are diagnosed in the vesicoureteric junction [8]. Stones located in the bladder are considerably less frequent in populations with high socioeconomic levels, with a prevalence of less than 10%.

The locality of the stone in the urinary tract greatly determines the treatment approach. Ureteroscopy (URS) has already been established as a treatment option for urolithiasis. To date, many studies have reported its increasing role not only in treating standard ureteric and renal calculi but also in patients with more complex stone disease or with co-morbidities [9]. Ureteroscopic lithotripsy (URSL) is the method of first choice for the management of ureteral stones, with an overall stone-free rate between 77% and 97.5% [10]. URSL does not require breaking the anatomical barriers of the urinary system. Therefore, it is relatively safe and easy to perform.
According to the current European Association of Urology (EAU) Guidelines, flexible URS should be used in cases where percutaneous nephrolithotomy or SWL are not an option (even for stones >2 cm). Additionally, they strongly recommend holmium:yttrium-aluminum-garnet laser (Ho:YAG laser) lithotripsy as the most effective treatment for all kinds of stones [11]. However, despite its many advantages, this procedure is not free from complications, including the postoperative development of urinary tract infection (UTI) [12]. In some scenarios, UTI after URSL might progress to urosepsis and further to septic shock with severe organ failure or even death [5]. Therefore, a prompt diagnosis of urosepsis is mandatory to administer effective and timely treatment. Thus, familiarity with risk factors for urosepsis might help to identify patients who are at a high risk of this serious complication. So far, many studies have investigated complications following URSL and identified risk factors of post-URSL infectious complications, including urosepsis [12–16]. However, considering the changing pattern of urolithiasis worldwide, these factors should be continuously analysed and established in each urological department. Therefore, in the presented study, we aimed to assess the incidence of urosepsis in patients undergoing URSL at the Department of Urology and Urological Oncology of Pomeranian Medical University in Szczecin. Furthermore, we investigated the potential risk factors for urosepsis that could be used as predictors of its development in the postoperative period.

MATERIAL AND METHODS

Study methods

This single-centre, retrospective study was exempt from further review by the Institutional Review Board (Bioethical Committee) of the Pomeranian Medical University, Szczecin, Poland, due to the nature of the study, and it was conducted according to the regulations set forth in the Declaration of Helsinki. Consent for research participation was routinely obtained from all patients involved for the use of their anonymized medical data collected during hospitalization. The study population included all consecutive patients with urinary stone disease who underwent URSL in 2022 at our Urology Department.

Preoperative evaluation

Patients qualified for elective procedures underwent preoperative assessment one week before their operation and had a routine mid-stream sample of urine (MSSU) sent for culture. Patients with a positive MSSU were treated with a 5-day course of an appropriate antibiotic according to their sensitivities. Antibiotic therapy was continued throughout hospitalization up to a complete 7-day course. Repeat samples of urine were not routinely obtained to confirm clearance if there were no symptoms of ongoing infection. In cases of emergency surgery, MSSU was sent for culture on the day of admission, and prophylactic antibiotic therapy was administrated. Cefuroxime was used in a prophylactic setting and was switched to targeted therapy if the urine culture was positive. Abdominal ultrasonography and non-contrast-enhanced computed tomography (CT) were performed in all patients before URSL to assess the presence of hydronephrosis and stone burden. For each patient, the following preoperative data were collected from medical records: age, sex, body mass index, concomitant diseases (diabetes mellitus and hypertension), previous history of urosepsis and endoscopic urological treatment, results of urinalysis and urine culture, stone size, location, and laterality, number of stones, stone density (measured in Hounsfield units), and hydronephrosis. Additionally, procedural time, length of stay (LoS), and the presence of residual fragments after URSL were evaluated. Moreover, if urosepsis occurred, blood cultures were collected to identify the pathogen and analyse the most common aetiological factors of post-URSL urosepsis in our department.

The surgical technique

All URSL procedures were performed with a semi-rigid 8.6/9.8F ureteroscope (Olympus) under general or spinal anaesthesia. To improve vision during the endoscopy a manual irrigation pump was used. After identification of the ureteral orifice, a flexible-tip 0.035-inch guidewire was introduced into the ureter and followed into the renal collecting system under X-ray supervision. Then, using guidewires, ureteroscopy was performed until ureteral

stones were localized. A single-use laser fibre and the Ho:YAG laser device were used for lithotripsy. The energy was applied at the setting of 1.0–1.5 J at a pulse rate of 10–15 Hz. A 6F double-J stent was routinely placed at the end of URSL and was extracted 5 days after the operation.

Follow-up

After the endoscopic procedure, the patients were prospectively observed for 30 days. The incidence of postoperative urosepsis was noted. Parameters such as temperature >38°C or <36°C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute or $PaCO_2$ <4.3 kPa, and white blood cell (WBC) count over 12×10^9/L or below 4×10^9/L were indicators of possible sepsis [17]. However, because sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, the diagnosis of urosepsis was based on the current definition. Therefore, organ dysfunction was identified as an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, with co-occurrence of confirmed or suspected infection of urinary tract origin [18, 19, 20]. The infection of urinary tract origin was confirmed by positive urine culture, whereas suspected UTI was defined as sterile pyuria (>400 WBC/μl) with inhibitory substances present (in-keeping with antibiotic use) and a C-reactive protein (CRP) over 10 mg/L, or the above plus a positive blood culture [21].

Statistical analysis

Two independent reviewers checked the obtained data for internal consistency. Descriptive statistics included mean and standard deviation (SD) for normally distributed data. Qualitative data were presented as numbers. Univariable and multivariable logistic regression analyses were used to examine the association of collected variables with the incidence of urosepsis after URSL. The odds ratios (ORs) were estimated with their 95% confidence intervals (CIs). V-fold cross-validation was used to build logistic regression models. The calibration was assessed with the Hosmer-Lemeshow goodness of fit test. We considered p value < 0.05 as statistically significant, and all p values were two-sided. All tests were performed using StatSoft statistical software, version 13.5 (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

A total of 231 patients undergoing URSL were enrolled in this study. The mean age of the patients

Table 1. *Patients' baseline characteristics.*

Variables	Study population (n = 231)	% of the study population
Age, years		
Mean	56.41	–
SD	13.72	–
Gender		
Female	92	39.83
Male	139	60.17
BMI, kg/m^2		
<30	174	75.32
≥30	57	24.68
Hypertension		
No	119	51.52
Yes	112	48.48
Diabetes mellitus		
No	192	83.17
Yes	39	16.88
Length of stay, days		
Mean	2.7	–
SD	1.32	–
Previous history of endoscopic treatment of urolithiasis		
No	150	64.94
Yes	81	35.06
Previous history of urosepsis		
No	220	95.24
Yes	11	4.76
Positive preoperative culture		
No	192	83.12
Yes	39	16.88
Multidrug-resistant pathogen		
No	223	96.54
Yes	8	3.46
Hydronephrosis		
No	178	77.06
Yes	53	22.94
DJ/PCN		
No	186	80.52
Yes	45	19.48
No. stones		
Single	182	78.79
Multiple	49	21.21
Maximum diameter of calculi, mm		
≤10	148	64.07
>10	83	19.48
Location of calculi		
Upper ureter (including UPJ)	59	25.54
Middle ureter	55	23.81
Lower ureter	83	35.93
Laterality of calculi		
Right	88	38.10
Left	138	59.74
Bilateral	5	2.16
Mean CT attenuation value of calculi, HU		
<500	95	41.13
500–1000	95	41.13
>1000	41	17.75
Presence of residual fragments after URSL		
No	123	53.25
Yes	108	46.75

Table 1. *Continued*

Variables	Study population (n = 231)	% of the study population
Operative time, minutes		
<30	117	50.65
30–60	86	37.23
>60	28	12.12
Postoperative urosepsis		
No	220	95.24
Yes	11	4.76

SD – standard deviation; BMI – body mass index; DJ – double-J stent; PCN – percutaneous nephrostomy; UPJ – ureteropelvic junction; CT – computer tomography; HU – Hounsfield units; URSL – ureteroscopic lithotripsy

Table 2. *Pathogens isolated from blood culture in patients with urosepsis.*

Pathogen causing urosepsis	Population with urosepsis (n = 11)	% of the urosepsis population
Escherichia coli	4	36.36
Pseudomonas aeruginosa	3	27.27
Klebsiella pneumoniae	1	9.09
Klebsiella oxytoca	1	9.09
Enterococcus faecalis	1	9.09
Proteus mirabilis	1	9.09

was 56.41 ±13.72 years, and the female-to-male ratio was 2:3. The general characteristics of the study population are presented in Table 1. Lifestyle diseases, which can be a risk factor for urinary stone disease, such as obesity, hypertension, or diabetes mellitus were present in 24.68%, 48.48%, and 16.88% of the study population, respectively. The length of stay deviated between 2 and 14 days, with a mean duration of 2.7 ±1.32 days.

During the 30-day follow-up of the study population, 11 patients (4.76%) developed urosepsis after URSL. Of these 11 patients, 6 were male and 5 were female, with a mean age of 66.66 years. Out of 11 patients with urosepsis, 3 (27.27%) had obesity (BMI >30 kg/m^2), 8 (72.72%) had hypertension, 4 (36.36%) had diabetes mellitus, and 9 (81.81%) had a previous history of endoscopic treatment of urolithiasis. However, only one patient with post-URSL urosepsis had been previously diagnosed with urosepsis ($p = 0.499$). The most common pathogen identified in the urosepsis population was Escherichia coli. Other pathogens isolated from blood culture are presented in Table 2. Whereas a multidrug-resistant (MDR) pathogen was found in 3 out of 11 patients. Urosepsis in all patients was diagnosed within 2 days of the surgery. All patients with post-URSL urosepsis suffered from fever > 38°C. Additionally, other clinical symptoms

Table 3. *Multivariable statistical analysis regarding the assessment of the association between the analysed parameters and the development of urosepsis in the 30-day post-procedure period.*

Variables	OR	Upper 95% CI	Lower 95% CI	p-value
Age	1.010	0.966	1.056	0.661
Gender				
Male	Ref.			
Female	1.274	0.377	4.303	0.967
BMI, kg/m^2				
<30	Ref.			
≥30	1.153	0.295	4.500	0.838
Hypertension				
No	Ref.			
Yes	2.974	0.769	11.509	0.114
Diabetes mellitus				
No	Ref.			
Yes	3.020	0.839	10.869	0.091
Previous history of urosepsis				
No	Ref.			
Yes	2.100	0.244	18.052	0.499
Positive preoperative culture				
No	Ref.			
Yes	6.800	1.962	23.573	0.003
Multidrug-resistant pathogen				
No	Ref.			
Yes	16.125	3.269	79.541	0.001
Hydronephrosis				
No	Ref.			
Yes	0.323	0.040	2.584	0.287
DJ/PCN				
No	Ref.			
Yes	3.750	1.090	12.898	0.036
No. stones				
Single	Ref.			
Multiple	0.818	0.171	3.915	0.801
Maximum diameter of calculi, mm				
≤10	Ref.			
>10	1.020	0.290	3.592	0.975
Location of calculi				
Upper ureter (including UPJ)	Ref.			
Middle ureter	1.077	0.208	5.575	0.930
Lower ureter	1.197	0.275	5.214	0.811
Laterality of calculi				
Right	Ref.			
Left	6.797	0.855	54.060	0.070
Bilateral	0.000	0.000	0.000	0.998
Mean CT attenuation value of calculi, HU				
<500	Ref.			
5000–1000	0.791	0.206	3.042	0.733
>1000	0.923	0.172	4.964	0.926
Operative time, minutes				
<30	Ref.			
30–60	0.669	0.162	2.752	0.577
>60	1.423	0.272	7.457	0.676

OR – odds ratio; CI – confidence interval; BMI – body mass index; DJ – double-J stent; PCN – percutaneous nephrostomy; UPJ – ureteropelvic junction; CT – computer tomography; HU – Hounsfield units

manifested in urosepsis patients included chills, nausea, vomiting, lower abdominal pain, and haematuria. Blood tests were performed in all symptomatic patients. In 10 cases WBC count was over 12×10^9/L. Whereas in one case the WBC count was below 4×10^9/L. If urosepsis was suspected, volume resuscitation was administrated along with intravenous antibiotic therapy with a broad spectrum of antimicrobial activity. All patients with diagnosed urosepsis had implantation of a double-J ureteral stent at the time of URSL. One patient did not respond well to conservative treatment and presented hydronephrosis in ultrasonography despite the inserted double-J stent. In this patient, the ureteral stent was extracted and a new one was implemented. No patient presented vasopressor-refractory shock and required further treatment in the intensive care unit. Moreover, no patient died during the 30-day follow-up.

Univariable analysis of the obtained data revealed that 3 factors were significantly associated with the risk of postoperative urosepsis, which increased if the double-J stent was inserted before URSL (OR 3.750; 95%CI (1.090–12.898; p = 0.036), the patient had a positive urine culture (OR 6.800; 95%CI, 1.962–23.573; p = 0.003) and MDR pathogen was found preoperatively (OR 16.125; 95%CI, 3.269–79.541; p = 0.001), Table 3. To further determine the risk factors for urosepsis after URSL, variables significantly associated with the risk of postoperative urosepsis in univariable analysis were selected for multivariable analysis. In the further analysis, only positive urine culture remained significantly associated with the risk of postoperative urosepsis incidence, with corresponding OR 6.800; 95%CI 1.962–23.573; p = 0.003.

DISCUSSION

The URSL is the first common application of upper urinary tract endoscopy. In the evolution of this technique, new instruments are being systematically introduced. Smaller and more precise instruments were continuously popularized to cause less trauma to normal tissues. Progress in endourology resulted in the introduction of fibreoptic-based rigid endoscopes with a diameter of 8 F on average. This facilitates the passing of a ureteroscope through a narrow and delicate distal ureter without forceful balloon dilations [22, 23, 24]. Currently, small rigid ureteroscopes combined with both laser and pneumatic lithotripters are used to treat ureteral stones. Mastery of this technique has allowed us to proceed with endourology while minimizing complications. However, despite the new, smaller, semirigid ureteroscopes, this minimally invasive surgery can be traumatic. The overall rate of complications after URSL varies between 9% and 25% [25]. According to the available literature and our own experience, most intraoperative incidents such as mucosal injury, ureteral perforation, extra-ureteral stone migration, or bleeding require only double-J insertion. However, early postoperative adverse events usually are more serious and often require readmission. Urosepsis is one of the most life-threatening possible consequences of URSL. It is noted in as many as 10% of patients in early post-operative follow-up and is related to the underlying pathology and morbidity of patients rather than to the applied endourological treatment. Therefore, considering changing trends in the prevalence and composition of urinary stones, patient demographics and risk factors of urosepsis after URSL should be routinely evaluated to enable adequate and timely treatment of urosepsis. Thus, in our study, we reassessed the influence of known preoperative and intraoperative factors on the risk of urosepsis after endoscopic treatment of ureteral stones.

The urosepsis in our cohort was diagnosed in 11 of 231 patients, constituting 4.76% of the study population. According to the largest systematic review with meta-analysis, performed by Bhojani et al., the urosepsis ratio after URSL varies from 0.2% to 17.8%, with a pooled incidence of 5.0% (95%CI 2.4–8.2) [13]. However, the studies included in this meta-analysis differ in diagnostic criteria of urosepsis, and some studies restricted the follow-up to in-hospital stay. Additionally, urosepsis occurred in the same number of patients after performing URSL in our clinic as the patients reporting its occurrence in their past medical history. Nevertheless, among 11 patients with urosepsis diagnosed in the 30-day follow-up, only one subject had previously been diagnosed with this condition. Statistical analysis revealed that a previous history of urosepsis did not significantly contribute to the more frequent incidence of urosepsis in our study population (OR 2.100; 95%CI 0.244–18.052; p = 0.499).

Statistical analysis also revealed that positive MSSU before URSL was significantly associated with the incidence of post-surgery urosepsis. These results are consistent with studies conducted by other researchers. Ma et al. in their meta-analysis reported that patients with positive preoperative urine culture were at a higher risk of septic complications, with pooled OR 2.18; 95%CI (1.34–3.57) [14]. These results may be attributed to the fact that bacterial infection of the urinary tract combined with the insertion of the ureteroscope during the procedure and normal saline washing enables many bacteria to enter the upper urinary tract and the bloodstream through injuries in the mucous membrane. What is more,

it is thought that performing retrograde pyelography at the time of initial management of obstructing ureteral stones with concomitant UTI might cause pyelovenous backflow of bacteria, thereby additionally accelerating the risk of urosepsis [26]. Moreover, urologists should always bear in mind that in the setting of obstructing ureteral stones renal forniceal rupture might be present before URSL, which in the case of UTI might be associated with severe morbidities, including perinephric abscesses and urosepsis [27].

Another explanation for the higher risk of urosepsis in patients with positive urine culture after URSL, despite definitive antibiotic therapy and controlling UTI before surgery, might be the presence of the MDR pathogen. Bai et al. did not find a significant association between positive preoperative urine cultures and post-URSL urosepsis. However, they observed that positive preoperative MDR urine culture was significantly associated with postoperative urosepsis despite proper preoperative antibiotic therapy, with corresponding OR 5.090; 95%CI (1.312–19.751). Additionally, they confirmed their results in matched-pair analysis [28]. In our study, overall, 39 (16.88%) of 231 patients had a positive preoperative urine culture. Out of these 39 patients, 8 (20.5%) had MDR pathogens. In the non-urosepsis group, 5 (2.27%) patients had a positive pre-operative MDR urine culture. In the urosepsis group, 3 (27.3%) patients had a positive preoperative MDR urine culture. However, univariable logistic regression analysis indicated that MDR pathogen-related UTI before URSL was a risk factor of postoperative urosepsis, with corresponding OR 16.125; 95%CI (3.269–79.541).

In the univariable analysis, we found that preoperative urinary tract decompression by ureteral stent or nephrostomy tube significantly increased the risk of post-URSL urosepsis, with corresponding OR 3.750; 95%CI (1.090–12.898). However, this result was not confirmed in multivariable analysis. Comparable results were also presented by other authors. Pre-URSL stenting was a crucial determinant of UTI following URSL as well as for urosepsis, with corresponding OR 1.91; 95%CI (1.26–2.91) and 3.04; 95%CI (1.67–5.54), respectively [29, 30]. This is mainly attributed to a biofilm formation on the stents [31, 32]. The biofilm is characterized by multiple bacterial layers that are additionally protected by a thick exopolysaccharide layer excreted by the bacteria. The presence of the protective layer results in significant resistance to antimicrobial therapy. Moreover, such colonization is also observed even when the stent is placed under sterile conditions and is mostly associated with dwelling time [32]. An additional mechanism that leads to the more frequent development of urosepsis with current ureteral stents is vesicoureteral reflux (VUR). The frequency of naturally occurring VUR is not fully investigated [33], but VUR occurring with a current double-J stent is a common finding. This mechanism promotes the spread of infection from the bladder to the renal collecting system [34]. Moreover, VUR might also increase intrapelvic pressure, which additionally promotes the entry of pathogens into the renal parenchyma [35]. Furthermore, the presence of the stent reduces the peristaltic movements of the ureteral musculature, which might also promote bacterial movement to the upper urinary tract [35].

Despite these interesting findings, our study has several limitations. Firstly, this is a single-centre study with a relatively small sample size. Conducting similar studies in other academic centres would enable a more profound and thorough analysis of the problem presented in our study and more reliable conclusions to be drawn. Secondly, our study was restricted by constraints inherent to the retrospective nature of the data analysis. Therefore, we were unable to control all preoperative confounding factors that may have influenced the risk of postoperative urosepsis such as stone composition, stone impaction, stone culture, or pelvis urine culture. Additionally, our study population included only patients with ureteral stones. Hence, we did not analyse the influence of other stone locations in the urinary tract on the incidence of urosepsis after endoscopic treatment. Finally, we did not analyse the stone-free rate, which may also have had a significant impact on patients' postoperative recovery. Authors should discuss the results and how they can be interpreted from the perspective of previous studies and the working hypotheses. The findings and their implications should be discussed in the broadest possible context. Future research directions may also be highlighted.

CONCLUSIONS

Patients with positive urine culture before URSL are at significantly higher risk of urosepsis in the postoperative period. Therefore, urine culture should be routinely performed on every patient before the planned endoscopic treatment of urolithiasis. Moreover, targeted antibiotic therapy before URSL does not eliminate this risk. Therefore, urologists should have increased awareness of this serious complication despite adequate preoperative treatment.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

UROLITHIASIS

Heavy as a rock or light as dust: a comparison between the perceived workload for extracorporeal shockwave lithotripsy, ureterorenoscopy and percutaneous nephrolithotomy

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Introduction There are three common treatment options for kidney stones: extracorporeal shockwave lithotripsy (ESWL), ureterorenoscopy (URS) and percutaneous nephrolithotomy (PNL). The choice of treatment is based on stone- and patient-related characteristics. However, some stones are eligible for several approaches and the decision is made based on patient and urologist's preferences. This study evaluates which approach has the highest workload.

Material and methods Between March and August 2022, five members of the Amsterdam Endourology Research Group collected data from 22 ESWL, 31 URS and 22 PNL procedures. After each procedure, the SURG-TLX questionnaire was completed by the surgeon to evaluate workload. Six dimensions were scored for each procedure, including: mental demands, physical demands, temporal demands, task complexity, situational stress, and distractions. The total workload, and the median for each dimension, was calculated and compared for the three treatments.

Results ESWL scored significantly lower than URS for mental demands, physical demands, temporal demands, situational stress, distraction and total workload. However, task complexity did not differ significantly between the two techniques. Compared with PNL, ESWL scored significantly lower for all dimensions. Finally, PNL received significantly higher scores for mental demands, physical demands, temporal demands, situational stress, distractions and total workload than URS. Only task complexity showed no significant difference between both groups.

Conclusions Urologists perceive the highest workload during PNL, followed by URS and finally ESWL. A follow-up study is needed to identify stressors that increase perceived workload with the purpose to address these variables and as final objective to improve urologists' workload, patient safety and treatment outcomes.

Key Words: endourology ‹› extracorporeal shockwave lithotripsy ‹› percutaneous nephrolithotomy ‹› SURG-TLX ‹› ureterorenoscopy ‹› workload

INTRODUCTION

Kidney stone disease is one of the most common urological disorders worldwide. The reported estimated overall prevalence of urolithiasis is currently 5–14% in Europe, 7–13% in the United States, and 1–5% in Asia and the incidence is still increasing [1, 2, 3]. The European Association of Urology (EAU) recom-

mends three different approaches for the treatment of kidney stones: extracorporeal shockwave lithotripsy (ESWL), ureterorenoscopy (URS), and percutaneous nephrolithotomy (PNL). The choice of treatment is made based on various patient- and stone-related characteristics. However, some stones are eligible for several, even all, therapeutic approaches and the choice of treatment could then be made based on patient and urologist's preferences [4].

Additionally, there has been an increasing interest in surgeon's wellbeing more recently [5–8]. Several papers have investigated the role of ergonomics during stone-treatment [9, 10, 11]. A recent survey on practice patterns and rates of musculoskeletal pain among urologists treating kidney stones found that there is a broad variance in the adherence to ergonomic best practice. Furthermore, the study discovered high rates of musculoskeletal pain among urologists [11]. However, the perceived workload of a procedure depends on more than ergonomics alone. The Surgery Task Load Index (SURG-TLX) questionnaire, which assesses six dimensions (*mental demands, physical demands, temporal demands, task complexity, situational stress and distractions*) has been developed and validated to evaluate the impact of several stressors on the perceived workload of surgeons during surgery [12]. This questionnaire was based on the widely used National Aeronautics and Space Administration Task Load Index (NASA-TLX) [13]. Previous studies in the field of endourology have used or recommended the SURG-TLX questionnaire, but none have compared the perceived workload between ESWL, URS and PNL [14, 15, 16]. Identifying the procedures and stressors causing the highest workload may enable the implementation of simple interventions to reduce the perceived workload for urologists in the future and consequently improve patient safety and treatment outcomes. As a first step, this study aims to evaluate the perceived workload of the three most common stone-treatment approaches. Furthermore, it aims to compare these three approaches to determine which of these options received the highest scores on the six dimensions of the SURG-TLX questionnaire.

MATERIAL AND METHODS

Study design

This is a prospective, dual-centre study conducted between March and August 2022. Data was collected from consecutive ESWL, URS and PNL procedures for the treatment of kidney stones performed at the Amsterdam UMC (Amsterdam, the Netherlands) and the Alrijne hospital (Leiderdorp, the Netherlands) by members of the Amsterdam Endourology Research Group (AERG). Twenty-two ESWL procedures were performed at the Alrijne hospital, while 31 URS and 22 PNL procedures were performed at the Amsterdam UMC. The exact process of evaluation was previously described in detail by our research group [15]. The primary surgeon assessed workload using a 20-point visual scale, as illustrated in Figure 1, after each procedure, scoring six dimensions. The second part of the SURG-TLX was omitted for this study, as research has shown that there is little to no additional value to the attribution of weight to the different dimensions, especially in the field of endourology [15, 17, 18]. However, the participants completed the second part of the SURG-TLX questionnaire during data collection and this data is available upon request. The total workload was determined as the aggregate of the scores from the six dimensions [12].

Ethics

This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, as well as with the ethical standards of the institutional and/or national research committee (complying with the Dutch law

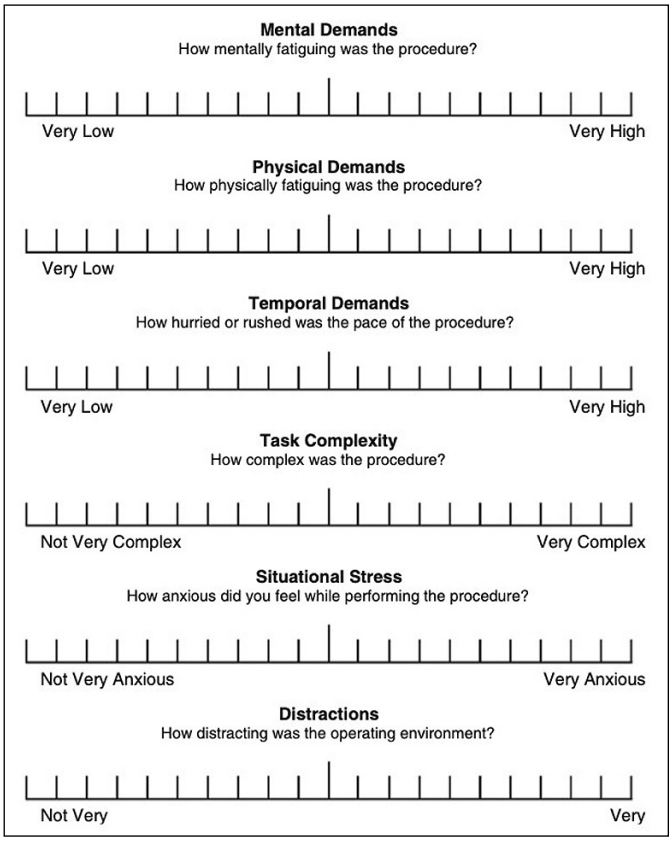

Figure 1. *Six dimensions, 20-point visual scale.*

on Medical Research in Humans: non-WMO-obligated due to the nature of the study).

Statistical analysis

Due to the lack of publications on this topic, a power-analysis to determine the sample size was not possible. Based on practical grounds, we decided to include procedures during a six month period, which resulted in 75 procedures.
Descriptive analysis was performed to determine workload per dimension for each stone-treatment approach. To provide a graphic representation of the data and to compare the distribution of our data, simple boxplots were used. Within the boxplots, outliers (1.5 x IQR) are displayed as circles and extreme values are displayed as asterisks (3 x IQR).
As all variables were continuous, outcomes were reported as medians and interquartile ranges (IQR). Normality of these continuous variables was checked with the Shapiro-Wilk test. Not all variables were normally distributed (Table 1). As non-parametric tests are valid for both non-normally distributed data and normally distributed data, we opted to use non-parametric tests to compare the results. Thus, the Kruskal Wallis-test and Mann-Whitney test were used to compare the results of the three stone-treatment approaches and determine statistical significance between the various dimensions. A two-sided p-value of ≤0.05 was considered statistically significant.
Statistical analysis was performed and boxplots were created using SPSS V.28 (IBM Corp., Armonk, NY, USA) and tables were created using Microsoft® Excel for Mac V.2016 (Microsoft Corp., Redmond, WA, USA).

Table 1. *A Shapiro-Wilk test of normality*

Dimension	Treatment approach	p-value
Mental demands	ESWL	<0.05
	URS	<0.05
	PNL	0.093
Physicial demands	ESWL	<0.05
	URS	<0.05
	PNL	0.195
Temporal demands	ESWL	<0.05
	URS	<0.05
	PNL	<0.05
Task complexity	ESWL	<0.05
	URS	<0.05
	PNL	<0.05
Situational stress	ESWL	<0.05
	URS	<0.05
	PNL	0.252
Distraction	ESWL	<0.05
	URS	<0.05
	PNL	0.172
Total workload	ESWL	<0.05
	URS	<0.05
	PNL	0.293

ESWL – extracorporeal shockwave lithotripsy; PNL – percutaneous nephrolithotomy; URS– Ureterorenoscopy

RESULTS

Five members of the AERG (ACB-H, JB, MMELH, NH and GMK), associated with the departments of Urology of the Amsterdam UMC (Amsterdam, the Netherlands) and the Alrijne hospital (Leiderdorp, the Netherlands), collected data for this study. A total of 75 procedures, of which 22 ESWL, 31 URS and 22 PNL, were included between March and August 2022.

Workload of the different treatment modalities

Figure 2 stone-treatment approach as simple boxplots. Compared to URS and PNL, ESWL had the lowest median mental demands (3.0/20 (IQR 2.0–4.3)), physical demands (2.5/20 (IQR 1.0–3.3)), temporal demands (1.5/20 (IQR 1.0–4.0)), task complexity (4.0/20 (IQR 3.0–5.3)), situation stress (1.0/20 (IQR 1.0–1.0)), distraction (1.0/20 (IQR 1.0–3.3)) and total workload (2.6/20 (IQR 1.9–3.4)).
URS received intermediate scores compared to ESWL and PNL for all dimensions. Median mental demands were 5.0/20 (IQR 3.0–8.0), median physical demands were 5.0/20 (IQR 3.0–7.0), median temporal demands were 4.0/20 (IQR 3.0–6.0), median task complexity was 6.0/20 (IQR 4.0–9.0), median situation stress was 4.0/20 (IQR 2.0–7.0), median distraction was 4.0/20 (IQR 3.0–6.0) and median total workload was 4.8/20 (IQR 3.3–7.7).
Finally, PNL had the highest median mental demands (7.5/20 (IQR 5.8–12.5)), physical demands (8.5/20 (IQR 6.0–12.0)), temporal demands (6.5/20 (IQR 5.0–9.5)), task complexity (7.0/20 (IQR 4.8–14.0)), situation stress (8.5/20 (IQR 5.8–13.3)), distraction (9.5/20 (IQR 6.0–14.0)) and total workload (8.2/20 (IQR 6.0–10.4)) compared to ESWL and URS.

Comparison between the different treatment modalities

A Mann-Whitney test showed a statistically significant difference between ESWL and URS concerning mental demands, physical demands, temporal demands, situational stress, distraction and total

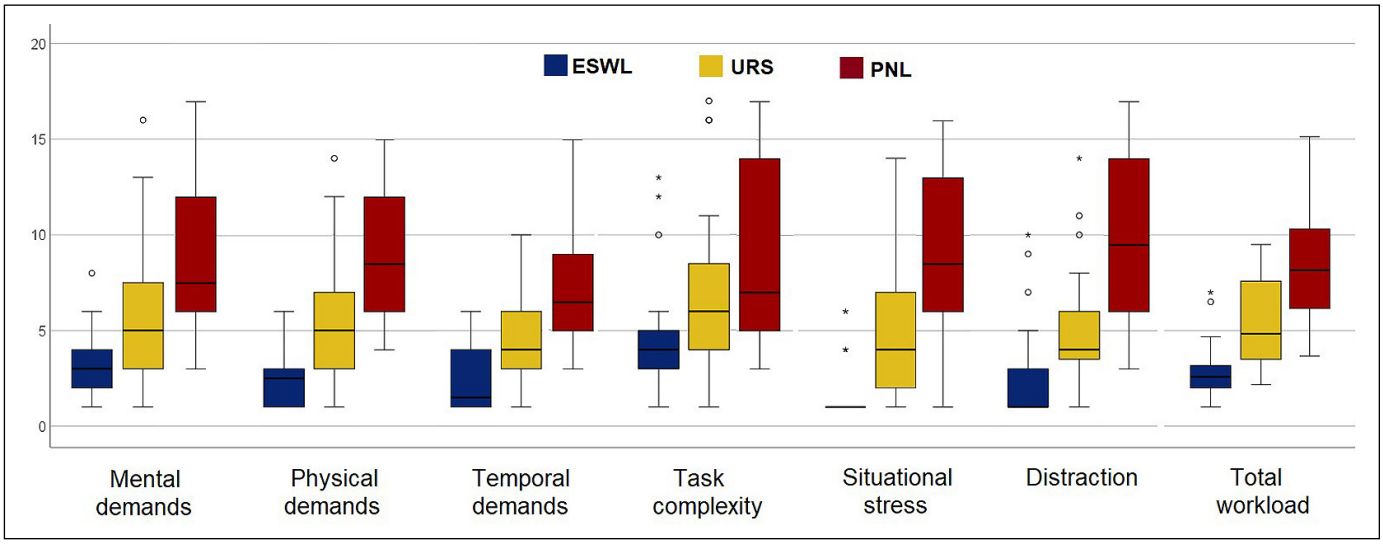

Figure 2. *The workload per dimension for each stone-treatment approach – boxplots.*

ESWL – extracorporeal shockwave lithotripsy; PNL – percutaneous nephrolithotomy; URS– Ureterorenoscopy

workload, as shown in Table 2. Yet, the task complexity was not different between both techniques (p = 0.07). Compared with PNL, ESWL scored significantly lower for all dimensions (p <0.05). PNL received significantly higher scores for mental demands, physical demands, temporal demands, situational stress, distractions and total workload than URS. Only task complexity showed no difference between both groups (p = 0.32).

Table 2. *Comparison between the different treatment modalities*

Dimension	ESWL - URS	ESWL - PNL	URS - PNL
Mental demands	<0.05	<0.05	<0.05
Physical demands	<0.05	<0.05	<0.05
Temporal demands	<0.05	<0.05	<0.05
Task complexity	0.07	<0.05	0.32
Situational stress	<0.05	<0.05	<0.05
Distraction	<0.05	<0.05	<0.05
Total workload	<0.05	<0.05	<0.05

ESWL – extracorporeal shockwave lithotripsy; PNL – percutaneous nephrolithotomy; URS– Ureterorenoscopy

DISCUSSION

This study shows that there is a clear difference in perceived workload when comparing the three treatment options for kidney stones that are recommended by the EAU: ESWL, URS, and PNL (Figure 3) [4]. Furthermore, this study compared these three approaches and found that PNL received the highest scores for all six dimensions of the SURG-TLX questionnaire.

Several factors can influence stone-free rates after stone-treatment. Not only stone and patient characteristics, but also surgeon experience and the chosen treatment modality can have an effect. According to the EAU guidelines, ESWL realises good stone-free rates for interpolar and upper pole stones up to two centimetres. And even though the stone-free rate is negatively affected by larger stone size and lower pole localisation, ESWL is not contra-indicated in these situations [4, 19–21]. Although stone-free rates are somewhat higher for URS when compared to ESWL for stones smaller than two centimetres, similar to ESWL, the stone-free rate of URS is negatively affected by increasing stone size and auxiliary treatments may be necessary to reach a stone-free status. Furthermore, URS is considered more invasive than ESWL and therefore shared decision making might lead to ESWL as the preferred choice of treatment [22]. Nonetheless, URS, and to a lesser extent ESWL, remain valid treatment options in stones larger than two centimetres, especially in patients who are not fit to undergo PNL [4, 22, 23, 24]. Even though, PNL remains the first choice for stones larger than two centimetres, as its stone-free rate is hardly affected by stone size [4].

Additionally to stone and patient characteristics, factors related to the surgeon, such as their experience and preference, influences the choice of treatment for kidney stones [25]. Until now, there is limited knowledge about the impact of surgeon preference on treatment selection, and the current focus is on patient-centred care, including shared decision making with extensive consideration for patient

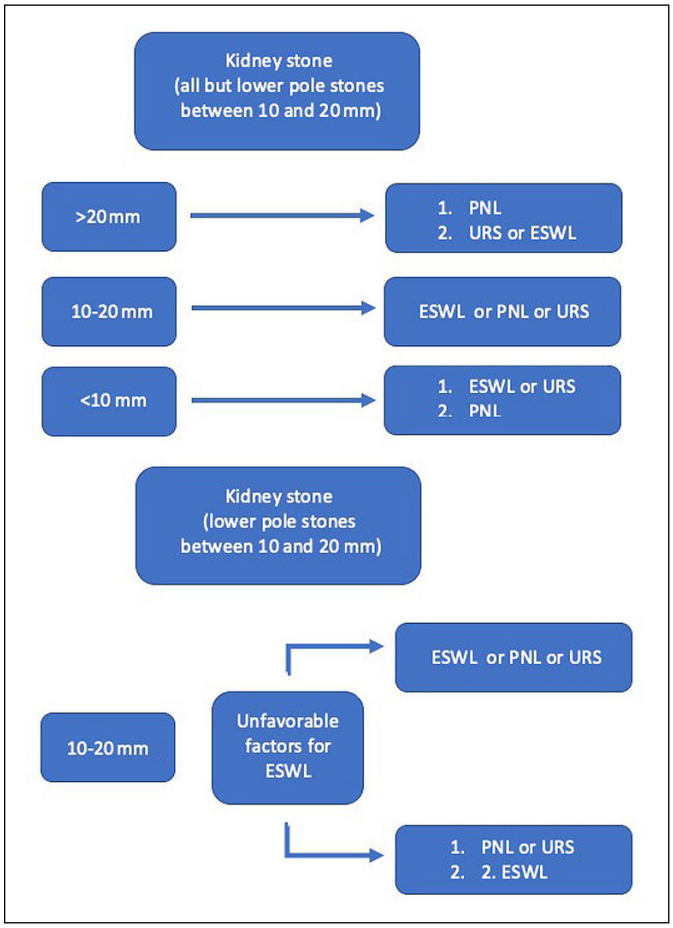

Figure 3. *The treatment options for kidney stones.*

ESWL – extracorporeal shockwave lithotripsy; PNL – percutaneous nephrolithotomy; URS– Ureterorenoscopy

preferences [26, 27, 28]. Physician burnout, however, is an important issue, especially in urology, with a considerable impact on the field [5, 29]. A study by Bohrer et al. on the quality of life of surgeons in Germany, found that 40% deemed their quality of life to be poorer than that of the general public [6]. According to Nauheim and North, an increase in workload, among other factors, leads to an increased burnout-rate [5]. Both studies concluded that measures should be taken to increase quality of life and prevent physician burnout [5, 6]. By taking the perceived workload of procedures into account, urologists could lower their workload and subsequently possibly influence the risk of burnout. Two systematic reviews investigated the effect of surgeon's wellbeing on patient outcomes and found an association between poor wellbeing and burnout of the surgeon and worse patient safety [7, 8]. Thus, by identifying procedures with a higher workload, as well as the stressors that increase the perceived workload, we could try to improve surgeon's wellbeing by addressing these stressors and this may subsequently help to improve patient safety and outcomes.

Until now, only two studies reported on the workload of stone-treatment with the SURG-TLX questionnaire. Hussain and colleagues evaluated the impact of flow disruption on mental workload and performance of surgeons during PNL. They divided this procedure into four steps and used a standardized tool to identify disruptions. Afterwards, they used the SURG-TLX questionnaire to assess the perceived workload and to correlate these results with the intraoperative interruptions. They concluded that the intraoperative disruptions were directly correlated with the surgeon's workload and had a detrimental effect on teamwork. Furthermore, they stated that reducing unnecessary disruptions and thus perceived workload, would lead to safer surgical care [16]. Our research group recently assessed if the SURG-TLX questionnaire is applicable for endourological procedures and set a first point of reference for perceived workload for these procedures. They included data on URS and PNL, however none on ESWL [15].

The current study is the first to assess the perceived workload of ESWL and compare the three most common stone-treatment options with one another. As one might expect, ESWL received the lowest and PNL the highest workload scores.

The most striking differences were found for the dimension of situational stress, where ESWL showed an extremely low median score of 1.0/20 (IQR 1.0–1.0) and PNL received a high median score of 8.5/20 (IQR 5.8–13.3). According to a systematic review and meta-analysis by Kallidonis and colleagues, the complication rate of ESWL seemed to be lower than for PNL [30]. Hence, the differences found in our study may be the result of the possible risks that are known to be inherent to a PNL procedure and consequently increases situational stress for the urologist. Risks that are not commonly associated with an ESWL procedure, thus possibly lowering the score for situational stress for this treatment modality.

Interestingly, the perceived task complexity did not differ between ESWL and URS ($p = 0.07$), nor did it differ significantly between URS and PNL ($p = 0.32$). However, the perceived task complexity was significantly lower for ESWL, when compared with PNL ($p < 0.05$). These results could be due to the fact that ESWL procedures were performed by participants in the beginning of their endourology career and PNL-procedures were performed by the more experienced members of the AERG. As the less experienced members are still in a learning curve, they might attribute more weight to task complexity, whereas the

contrary could be said about the more experienced members, who have already seen and lived it all.
To the best of our knowledge, this is the first study to evaluate the perceived workload for ESWL, URS and PNL and compare the results of these three stone treatment-options. Although this is a dual-centre, prospective study that gives an insight in the workload of the three main stone-treatment approaches, a future prospective multicentre study, including more participants and procedures, is needed to assess the true workload of these procedures. This study has some limitations, including the fact that it focused solely on the urologist's experience and did not include surgical outcomes in the equation. Additionally, it did not assess which variables influence the perceived workload, as the main goal was to identify which treatment modality had the highest workload. Therefore, a more in-depth evaluation of these three stone-treatment approaches, including the possible effect of external variables, is necessary to understand the perceived workload better. By identifying high workload procedures and stressors during these procedures that influence perceived workload, measure could be taken to lower workload for urologists. As described before, this could lead to less burnout and increased wellbeing for the urologist and consequently to improved patient safety and treatment outcomes. These findings then would require further interventional studies that address these stressors with a final objective to not only improve urologist's quality of life but also improve patient safety and treatment outcomes.

CONCLUSIONS

Each stone treatment modality has a different perceived workload. Urologists perceive the highest workload during PNL, followed by URS and ESWL when treating kidney stones. However, bigger cohorts are needed to balance out environmental and surgeon-specific variables. Furthermore, a better understanding of the perceived workload and the stressors influencing said workload may lead to interventions to enhance surgeons' working conditions and to subsequently improve patient safety and treatment outcomes.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

UROLITHIASIS

Retrograde intrarenal surgery using the ILY robotic flexible ureteroscope: a single centre experience

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Introduction The ILY robotic flexible ureteroscope has been introduced in order to improve intraoperative ergonomics, reduce operator distance from radiation and shorten the learning curve. In this study we aimed to assess the clinical performance and feasibility of the ILY robot during retrograde intrarenal surgery (RIRS) and combined endoscopic procedures (miniECIRS).

Material and methods The RIRS procedures were performed using the ILY robotic arm in 57 adult patients (46 RIRS and 11 miniECIRS) from 2022 to 2023. All procedures were performed in the supine position. Pre-stenting was not the standard of care.

Results Turning on and calibration of the device took approximately 100 s. Average draping time was 93 s using original ILY drapes and 47 s using classic drapes designed for C-arm covering. Mean docking time was 73 s in procedures with ureteral access sheath (UAS) and 61 s in procedures without it. The undocking took less than 60 s in every case. Average procedure time was 63 min for RIRS and 55 min for miniECIRS. Endoscopically proven stone-free rate was achieved in 37 (80.4%) RIRS and 10 (90.9%) miniECIRS patients. A total of 17 (36.9%) RIRS and 8 (72.7%) miniECIRS procedures required conversion in order to perform basketing and stone fragments retrieval/transposition.

Conclusions The use of ILY robot during endourological procedures is feasible and urologists that are familiar with the device controller do not require extensive training. The time needed for device draping, docking and undocking was approximately 4 minutes. Moreover, use of the robot resulted in satisfactory stone-free rates.

Key Words: urolithiasis ‹› kidney calculi ‹› RIRS ‹› ECIRS ‹› robotic endourology

INTRODUCTION

Robotic assisted flexible ureteroscopy (fURS) and retrograde intrarenal surgery (RIRS) have been developing rapidly in recent years. Classic robotic platforms cannot be used in any minimally-invasive endourological procedures, therefore, new robotic systems such as Sensei, Roboflex Avicenna, Easy-Uretero, Monarch, Virtuoso and ILY have been developed for kidney stone management [1–3].

In this study we aimed to assess the clinical performance and feasibility of the ILY robot during RIRS and combined endoscopic procedures.

MATERIAL AND METHODS

Informed consent was obtained from all participants prior to the surgical procedure. The study was approved by the Institutional Bioethics Committee of the Wrocław Medical University (consent number 16/KB/2023).

The RIRS procedures were performed using the ILY robotic arm in 57 adult patients (46 pure RIRS and 11 endoscopic combined intrarenal surgeries – flexible ureterorenoscope and percutaneous access of 15/16 Fr (miniECIRS)) from 2022 to 2023 by an experienced endourological team of the Department of Minimally Invasive Robotic Urology of Wroclaw Medical University.

Consecutive patients operated in our centre that presented with nephrolithiasis in normal renal anatomy were included. Patients with bulky staghorn stones or otherwise complex cases requiring more than one percutaneous access were not included. General criteria for RIRS procedure included solitary stone not bigger than 1.5 cm or multiple stones with maximal volume of 750 mm^3. More complex cases were usually treated with miniECIRS procedure.

Even though the staff have been adept in manipulating the device's controller before the onset of the study, the first 5 cases performed by our team were excluded from the analysis, as some training was necessary to get familiar with the device. Finally, 57 participants were included in this research.

Hawk flexible ureteroscopes and Quanta CyberHo 60 W holmium laser with 272 micron fibers were used during every RIRS. If UAS was used, 10.7 Fr sheet was employed, with various lengths. Percutaneous access was obtained under combined USG/fluoro control, and 12 Fr nephroscope with 16 Fr Amplatz and 272 microns laser fiber was used for all the miniECIRS procedures. All the procedures were performed in the supine position. Pre-stenting was not the standard of care.

Stone-free status was assessed perioperatively (endoscopically and fluoroscopically) and being stone-free was defined as no visible residual fragments bigger than 2 times the laser fiber diameter.

Demographic data were collected before the surgery. We evaluated the times needed to: turn on and calibrate, drape, dock and undock the ILY robot. Moreover, patients' clinical details were recorded [stone size, density and location, presence of the pre-operative double J (DJ) stent]. Finally, intraoperative data were documented (duration of the procedure, stone-free rate, need for conversion, need for post-operative DJ placement).

RESULTS

Main patients' characteristics are presented in Table 1. The study involved 57 patients with nephrolithiasis that underwent RIRS or miniECIRS procedures supported by the ILY robotic system. Mean age of patients was 46 years (range 18–82 years). For RIRS cases average stone size was 1.3 cm (range 0.8–2.3 cm), while for ECIRS procedures the mean biggest stone size was 1.9 cm (range 1.1–5.6). 37 (65%) patients were pre-stented (32 RIRS and 5 ECIRS cases). In order to assist calibration, draping and docking of the device, one additional briefly trained person (nurse/technician) was needed. Table 2 summarises the average times needed for preparation of the robot and the procedure. Average procedure time was 63 min (range 15–91 min) for RIRS (counting from the first insertion of the scope into the bladder to the bladder catheterisation) and 55 min (range 32–83 min) for miniECIRS (counting from the first insertion of the nephroscope into the kidney to the bladder catheterisation). In total, 34 (73.9%) RIRS and 4 (36.4%) miniECIRS procedures were performed with UAS, the majority in males.

Table 1. *Main patients' characteristics*

Clinical characteristic	Statistical feature
Mean age (SD; range)	46 (19.3; 18–82)
Male/Female	28/29
RIRS/miniECIRS	46/11
Mean biggest stone size in RIRS (SD; range)	1.3 cm (0.41; 0.8–2.3)
Mean biggest stone size in miniECIRS (SD; range)	1.9 cm (1.33; 1.1–5.6)
Mean stone density in RIRS (SD; range) [HU]	943 (264.6; 620–1430)
Mean stone density in miniECIRS (SD; range) [HU]	1101 (234.3; 716–1496)
Mean Guy's Stone Score	1.49
Mean fluoroscopy time in RIRS (SD; range)	1.9 s (4.4; 0–21)
Mean fluoroscopy time in miniECIRS (SD; range)	16 s (9.8; 1–38)
Pre-procedural DJ presence	64.9%
Post-operative DJ placement (RIRS)	67.4%
Post-operative DJ placement (miniECIRS)	63.6%

SD – standard deviation; RIRS – retrograde intrarenal surgery; miniECIRS – endoscopic combined intrarenal surgery; HU – Hounsfield units; DJ – double J

Table 2. *Average times needed for preparation of the robot and the procedure*

Action	Mean time (range)
Turning on and calibration	100 s
Draping (original ILY drapes)	93 s (69–229)
Draping (classic C-arm drapes)	47 s (23–71)
Docking (with UAS)	73 s (32–124)
Docking (without UAS)	61 s (30–99)
Undocking	<60 s
RIRS duration	63 min (15–91)
miniECIRS duration	55 min (32–83)

UAS – ureteral access sheath; RIRS – retrograde intrarenal surgery; miniECIRS – endoscopic combined intrarenal surgery

Perioperatively proven stone-free rate was achieved in 37 (80.4%) RIRS and 10 (90.9%) miniECIRS patients. A total of 17 (36.9%) RIRS and 8 (72.7%) miniECIRS procedures required robot undocking and conversion in order to perform basketing and stone fragments retrieval/transposition.
All miniECIRS cases received a nephrostomy 8 Fr drain that was removed on postoperative day one. Postoperative DJ stent was placed in 31 (67,4%) RIRS cases and in 7 (63,6%) miniECIRS cases.

DISCUSSION

The recent technological improvements in fURS have led to an increased use of endourological and combined procedures in urolithiasis [4]. These methods are characterised by high stone-free rates and low-invasiveness simultaneously. However, a long learning curve, as well as high radiation exposure and forced position of the surgeon performing these operations resulted in the search of improvement. In response to these issues, a few endourological robots have been introduced to the market.
The ILY robotic system is a remotely controlled ureteroscope holder manipulated by a simple gaming controller. The system allows the transmission of all basic flexible ureteroscopy (fURS) movements. Also, it is compatible with all commercially available digital flexible ureteroscopes and ureteral access sheaths (UAS) [2]. During RIRS, the remote control by ILY system is available after the manual introduction of UAS and fURS and their attachment to the receptacle. Throughout the operation, surgeon's position is restricted only by the distance from the device. The robot is characterized by wide rotational manoeuvrability (±360 degrees) – much higher when compared to other systems [2].
The ILY's system differs from the other robots significantly. Firstly, the gaming joystick is used to control the robotic arm, instead of a bulky master console. Gauhar et. al pointed out that the use of a video-game controller is not intuitive, as it does not reproduce the stereotypical hand movements performed during traditional fURS [2]. However, in our opinion, an immense number of people are already experienced in using such controllers, because of the popularity of video games. Moreover, such a solution allows for complete freedom of movements of the operator.
Secondly, the ILY robotic arm is the most compact and mobile of all systems. Due to the lack of master console and a small size of the receptacle, it takes little space in the operating theatre.
Up to date, no other studies involving humans regarding the use of ILY robot have been published [3]. In our research, stone-free rate was satisfactory and the average durations of the procedures were not significantly longer than in the standard approach. As a majority of the robot handling is performed in parallel to surgery, only docking and undocking prolongs the operation. Depending the clinical scenario, additional time needed because of ILY usage ranged between one and three minutes.
Nonetheless, the system has a few disadvantages. Firstly, the laser fiber adjustments and the stone basket manipulations need to be performed manually by the additional assistant. Secondly, there is no mechanism that allows for the control of the inflow and flushing of the irrigation solution. Finally, the ILY and other robots lack tactile feedback. However, the technology is being developed to incorporate force feedback into robotic fURS in the future [5].
We are aware that our study has some limitations. The trial was not comparative, so we could not prove the superiority or at least non-inferiority of robotic procedures over the standard approach. Also, a relatively low number of patients were included. Hence, this article possibly did not contain a complete cross-section of patients with kidney stones.
However, our report still has some clear strengths. It is the first research that used the ILY robotic arm in urolithiasis management. Moreover, the study was conducted in a large urologic centre that performs an immense number of standard RIRS and miniECIRS every year. That certifies the proficiency and repeatability of the procedures.

CONCLUSIONS

The use of ILY robot during endourological procedures is feasible and urologists that are familiar with the device controller do not require extensive training. The time needed for device draping, docking and undocking was approximately 4 minutes. Moreover, use of the robot did not prolong RIRS and miniECIRS procedures significantly and resulted in satisfactory stone-free rates.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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REVIEW PAPER

UROLITHIASIS

Regional versus general anaesthesia in percutaneous nephrolithotomy: a systematic review and meta-analysis

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Introduction Several studies have compared the safety and effectiveness of general and regional anaesthesia in percutaneous nephrolithotomy (PCNL). This study aimed to compare the perioperative and postoperative outcomes of general anaesthesia and regional anaesthesia for patients undergoing PCNL.

Material and methods For relevant articles, three electronic databases, including PubMed, Scopus, and Web of Science, were searched from their inception until March 2023. A meta-analysis has been reported in line with PRISMA 2020 and AMSTAR Guidelines. The risk ratio (RR) and mean difference (MD) were applied for the comparison of dichotomous and continuous variables with 95% confidence intervals (CI).

Results The final cohort analysis, comprised 3871 cases of PCNL, (2154 regional anaesthesia and 1717 general anaesthesia). Compared to general anaesthesia, the regional anaesthesia group had a significantly shorter length of stay (MD = -0.34 days, 95% CI -0.56 to -0.12, p = 0.002), lower postoperative nausea and vomiting rates (RR = 0.16, 95% CI 0.03 to 0.80, p = 0.026), lower complications grade III–V rates (RR = 0.68, 95% CI 0.53 to 0.88, p = 0.004), and lower postoperative visual analogue pain score (VAS) at 1 hour (MD = -3.5, 95% CI -4.1 to -2.9, p <0.001). There were no significant differences in other outcomes between the two groups.

Conclusions Our results show that PCNL under regional anaesthesia is safe and feasible, with comparable results to those done under general anaesthesia. While patient selection is important, counselling and decision-making for these procedures must go hand in hand to achieve the best clinical outcome.

Key Words: kidney calculi ‹› percutaneous nephrolithotomy ‹› PCNL ‹› regional anaesthesia

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is a minimally invasive procedure commonly used in Endourology and has become the standard for managing large and complex renal calculi [1]. From the first report by Fernstrom and Johansson in 1976, PCNL techniques have been modified to ameliorate safety, efficacy, and decrease morbidity [2].

In PCNL procedures, the choice of anaesthesia impacts the outcomes, especially in minimising respiratory complications and length of hospital stay. Both general anaesthesia and regional anaesthesia have their advantages. While general anaesthesia dominates in controlling patients' breathing and improving their comfort, regional anaesthesia has advantages with its lower rate of postoperative drug reactions and shorter procedural duration

and hospital stay [1]. Many studies have compared the safety and effectiveness of general and regional anaesthesia in the PCNL. However, the conclusions are inconsistent, and there is a lack of agreement on the optimal anaesthesia setting for PCNL. This study aimed to compare the perioperative and post-operative outcomes of general anaesthesia and regional anaesthesia for patients undergoing PCNL.

MATERIAL AND METHODS

Literature search

This study was conducted following the accepted methodology recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) [3,4]. Three electronic databases, Scopus, Web of Science (ISI), and PubMed were searched to identify relevant studies regarding perioperative and post-operative outcomes of patients undergoing PCNL under regional anaesthesia or general anaesthesia from January 1980 to March 2023. The search terms included combinations of 'local', 'regional', 'locoregional', 'loco-regional', 'nerve' with 'anesthesia', 'anaesthesia', 'analgesia', 'block' and 'PCNL', 'percutaneous nephrolithotomy', 'percutaneous nephrolithotomy', 'percutaneous nephrolithotripsy', 'percutaneous stone lithotripsy', 'ECIRS', 'endoscopic combined intrarenal surgery', 'miniPCNL', 'mini-PCNL', 'microPCNL' and 'micro-PCNL'. Boolean operators (AND, OR) were used to refine the search. Additionally, we performed a manual search of references from articles included in Scopus, PubMed and Web of Science to avoid missing any relevant publications, and from reference lists of included articles [5].

Selection criteria and abstract screening

Inclusion criteria

1. Original articles reporting on the peri and postoperative outcomes of PCNL under anaesthesia.
2. Studies in the English language with a minimum of 20 patients.

Exclusion criteria

1. Not relevant to the study topic, in vitro or animal study
2. Review articles, book chapters, thesis
3. Conference papers, editorials, letters, oral presentations, correspondences, communications, and posters
4. Studies were done under regional anaesthesia where data on regional anaesthesia could not be separated from those who underwent general anaesthesia
5. Studies examining PCNL for non-urolithiasis conditions or ureteral stones
6. Studies that explicitly did not report SFR.

Two independent groups of reviewers (MS, TTN) performed title and abstract screening to select relevant papers. Eligible publications were further screened for inclusion in the systematic review and meta-analysis. Any disagreement was resolved by discussion and consensus (MS, TTN, BKS) if necessary.

Full-text screening and data extraction

Regarding data extraction, two authors (MS and TTN) developed the extraction form using Excel (Microsoft Corp., Redmond, WA, USA). All disagreements and discrepancies were resolved by discussion and consensus. Papers published by the same research group were checked for potential overlapping data based on the period of case recruitment, the center where the cases were recruited, and confirmation from the study authors when necessary. For those studies that selected patients from the same institutions or databases, we chose the studies with the highest number of patients or the most recent data for the primary analyses.

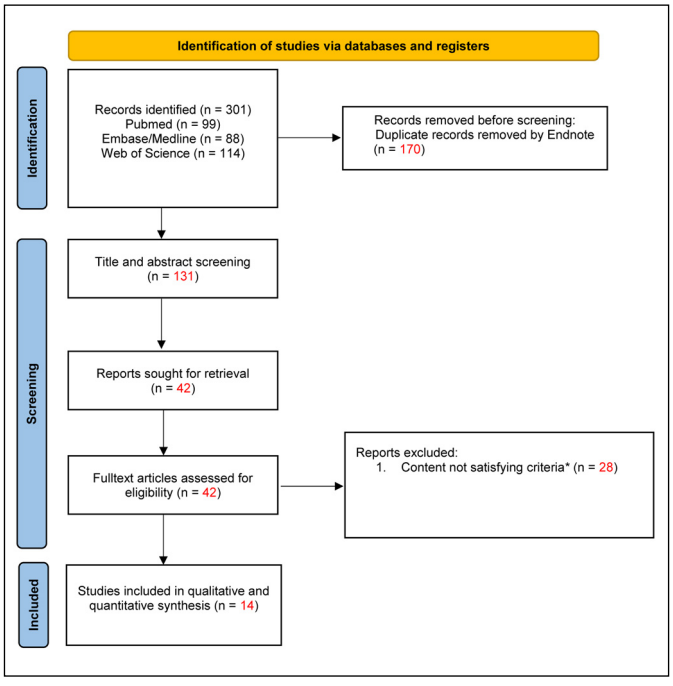

Figure 1. *Evidence acquisition flow chart.*

*Records excluded due to single-arm study design or lack of information related with perioperative outcomes

**Includes no reliable or overlapped data.

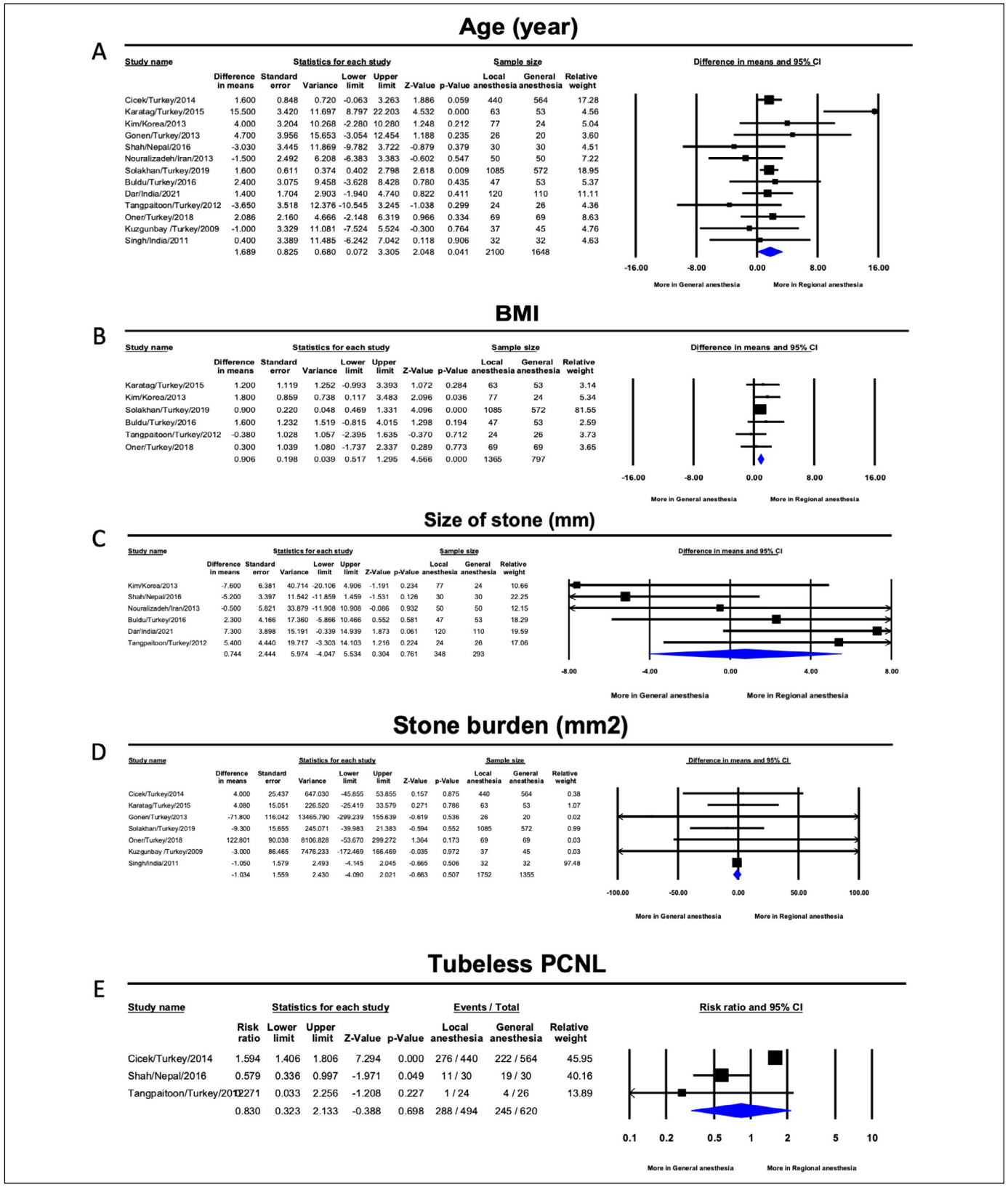

Figure 2. *Forest plots for the meta-analysis comparing the characteristics of percutaneous nephrolithotomy patients between regional anesthesia and general anesthesia groups:* **(a)** *Age;* **(b)** *BMI;* **(c)** *Size of stone;* **(d)** *Stone burden,* **(e)** *Tubeless percutaneous nephrolithotomy.*

PCNL – percutaneous nephrolithotomy

Table 1. *Characteristics of included studies*

Study ID (Author/Year/ Country)	Study design	No. of patients	Regional anesthesia	No. of cases		Percentages of males		Sedation		Position	Type of puncture	Type of lithotriptor	Sheath size (Fr)	Age (years)		BMI		ASA		Stone diameter (mm)		Stone burden (mm²)	
				Regional	General	Regional	General	Regional	General					Regional	General	Regional	General	Regional	General	Regional	General	Regional	General
Singh/India /2011 [9]	Randomized	64	L1–L2	32	32	NA	NA	no	no	Prone	Fluroscopy guidance	pneumatic	30	40	39.6	NA	NA	NA	NA	21.9	22.7	NA	NA
Kuzgunbay/Turkey/2009 [10]	Randomized	82	L3–L4	37	45	64.9	57.8	no	no	Prone	Fluroscopy guidance	pneumatic	30	44	45	NA	NA	NA	NA	NA	NA	731	734
Moslemi/ Iran/2012 [11]	Retrospective	123	L–2L3	54	69	NA	NA	NA	NA	Prone	Fluroscopy guidance	pneumatic	30–32	39	41	25	26	NA	NA	NA	NA	NA	NA
Oner/Turkey /2018 [12]	Retrospective	138	catheter at t12–L1, sensory level T6–S4	69	69	60.9	53.6	yes	no	Prone	Fluroscopy guidance	pneumatic	30	46.4	44.3	28.6	28.3	1.3	1.2	NA	NA	867.0	744.2
Tangpaitoon /Turkey/2012 [13]	Randomized	50	L1–L2	24	26	70.8	61.5	NA	NA	Prone	Fluroscopy guidance	pneumatic	30	53.0	56.6	21.2	21.6	23 (ASA 1–2), 1 (ASA 3)	25 (ASA 1–2), 1 (ASA 3)	40.8	35.4	NA	NA
Dar/India/2021 [14]	Prospective randomized	230	T9–T10or T10–T11	120	110	55.0	56.4	no	no	Prone	Fluroscopy guidance	laser/ Pneumatic	24–28	39.9	38.5	NA	NA	ASA 1–2	ASA 1–2	61.9	54.6	NA	NA
Buldu/Turkey /2016 [15]	Retrospective	100	L3–L4 (T4 dermato-me)	47	53	70.2	79.2	NA	NA	Prone	Fluroscopy guidance	pneumatic	30	48.5	46.1	28.7	27.1	1.4	1.2	52.9	50.6	NA	NA
Solakhan/Turkey /2019 [16]	Retrospective	1657	l2–l3	1085	572	66.6	59.6	no	no	Prone	Fluroscopy guidance	NA	30	34.3	32.7	25.1	24.2	128 (ASA 3)	106 (ASA 3)	NA	NA	635.2	644.5
Nouralizadeh/Iran /2013 [17]	Randomized	100	L3–L4, T6 dermato-me	50	50	58.0	54.0	no	no	Prone	Fluroscopy guidance	pneumati-c+laser	28–30	41.1	42.6	NA	NA	ASA 1–2	ASA 1–2	55.1	55.6	NA	NA
Gonen/Turkey /2013 [18]	Retrospective	46	L2–L3	26	20	69.2	65.0	no	no	Prone	Fluroscopy guidance	pneumatic	30	45.5	40.8	NA	NA	NA	NA	NA	NA	558.6	630.4
Shah/Nepal /2016 [19]	Randomized	60	l3–l4 (T6 dermatome)	30	30	43.3	63.3	yes	no	Prone	Fluroscopy guidance	pneumatic	26–30	36.1	39.1	NA	NA	ASA 1–2	ASA 1–2	32.3	37.5	NA	NA
Kim/Korea /2013 [20]	Retrospective	101	L3–4 or L4–5	77	24	61.0	58.3	yes	no	Prone	Ultrasound	ltrasonicand pneumatic lithotripsy	28–30	54.8	50.8	25.1	23.3	NA	NA	34.5	42.1	NA	NA
Cicek/Turkey /2014 [21]	Retrospective	1004	L2–L3	440	564	64.3	60.1	yes	no	Prone	Fluroscopy guidance	pneumatic	30	48.8	47.2	NA	NA	33 (ASA 3)	39 (ASA 3)	NA	NA	533	529
Karatag/Turkey /2015 [22]	Retrospective	116	L3–L4 or L4–L5; T4 dermatome	63	53	NA	NA	no	no	Prone	Fluroscopy guidance	laser	4.8	45.8	30.3	27	25.8	NA	NA	NA	NA	155.0	151

ASA – American Society of Anesthesiologists score; BMI – Body mass index; NA – Not available

Table 2. *Meta-analysis of the characteristics and perioperative outcomes of percutaneous nephrolithotomy patients between regional and general anesthesia groups*

Variables	No. of Studies	No. of patients		Heterogeneity		Overall effect	
		Regional	General	I^2 (%)	p-value	MD/RR (95% CI)	p-value
Age (year)	13	2100	1648	50	0.019	1.68 (0.07, 3.3)	0.041
BMI	6	1365	797	0	0.642	0.9 (0.51, 1.29)	<0.001
Size of stone (mm)	6	348	293	43	0.114	0.7 (-4.0, 5.5)	0.761
Stone burden (mm^2)	7	1752	1355	0	0.846	-1.03 (-4.09, 2.02)	0.507
Operative time (minute)	14	2154	1717	94	<0.001	-8.2 (-17.3, 0.8)	0.076
Length of stay (day)	12	2031	1579	89	<0.001	-0.34 (-0.56,-0.12)	0.002
Nephrostomy	2	470	594	0	0.863	0.61 (0.5, 0.7)	<0.001
Tubeless PCNL	3	494	620	86	0.001	0.83 (0.32, 2.13)	0.698
Need for auxiliary procedures	6	372	299	0	0.84	1.07 (0.7, 1.4)	0.678
Stone-free rates (SFR) at 1 month	14	2154	1717	0	0.923	1.01 (0.98, 1.03)	0.4
Blood transfusion	9	1827	1455	39	0.102	0.77 (0.5, 1.18)	0.231
Postoperative nausea and vomiting (PONV)	3	104	106	60	0.081	0.16 (0.03, 0.80)	0.026
Complications Grade I–II	14	2154	1717	38	0.07	0.98 (0.79, 1.21)	0.883
Complications Grade III–V	8	1883	1476	0	0.837	0.68 (0.53, 0.88)	0.004
Postoperative visual analog pain score at 1 hour	2	144	136	0	0.59	-3.5 (-4.1,-2.9)	<0.001
Postoperative visual analog pain score at 12 hours	2	144	136	0	0.708	-0.4 (-0.88, 0.03)	0.07
Postoperative visual analog pain score at 24 hours	2	144	136	0	0.885	-0.15 (-0.60, 0.30)	0.512
Opioid use	2	76	70	97	<0.001	-3.1 (-6.6, 0.3)	0.077

PCNL – percutaneous nephrolithotomy; CI – confidence interval; MD – mean difference; RR – risk ratio

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of studies included in our meta-analyses, in which stars were awarded for cohort or case-control studies (maximum nine stars) based on a developed checklist [6]. Studies that were awarded at least six stars were considered moderate- to high-quality studies, while those with a NOS value of less than six were regarded as low-quality studies [6].

Statistical analysis

A comprehensive Meta-analysis (Englewood, NJ, USA) was used for statistical analyses. Among-study heterogeneity was assessed by the I^2 statistic, which shows the total variation across studies that is not a result of chance [7]. An I^2 statistic ranging from 25–49%, 50–74%, and ≥75% indicates a low, moderate, and high heterogeneity, respectively [8]. Sensitivity or subgroup analyses were performed to handle heterogeneity. We used risk ratios (RR) with 95% confidential intervals (CI) for categorical variables. The pooled results are presented as a forest plot using random-effects models. Egger's regression test and funnel plot were calculated to assess the presence of publication bias. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Search results and study characteristics

A total of 301 articles were identified from three electronic databases, including Scopus, PubMed, and Web of Science. After screening those articles by title and abstract, 42 articles were selected for full-text assessment. Upon full-text review, 28 articles were excluded due to lack of proper information, study design, and duplication. In total, 14 articles that met the inclusion criteria were included in the final cohort analysis, comprising 3871 cases of PCNL, including 2,154 regional anaesthesia cases and 1717 general anaesthesia cases [9–22]. The evidence acquisition flow chart is shown in Figure 1. The individual characteristics of all included studies are described in Table 1.

Perioperative and postoperative outcomes after percutaneous nephrolithotomy

A summary of this meta-analysis of the characteristics and outcomes of two groups (regional anaesthesia and general anaesthesia) is demonstrated in Table 2. Compared to general anaesthesia, the regional anaesthesia group had a significantly higher age (MD = 1.68 years, 95% CI 0.07 to 3.30,

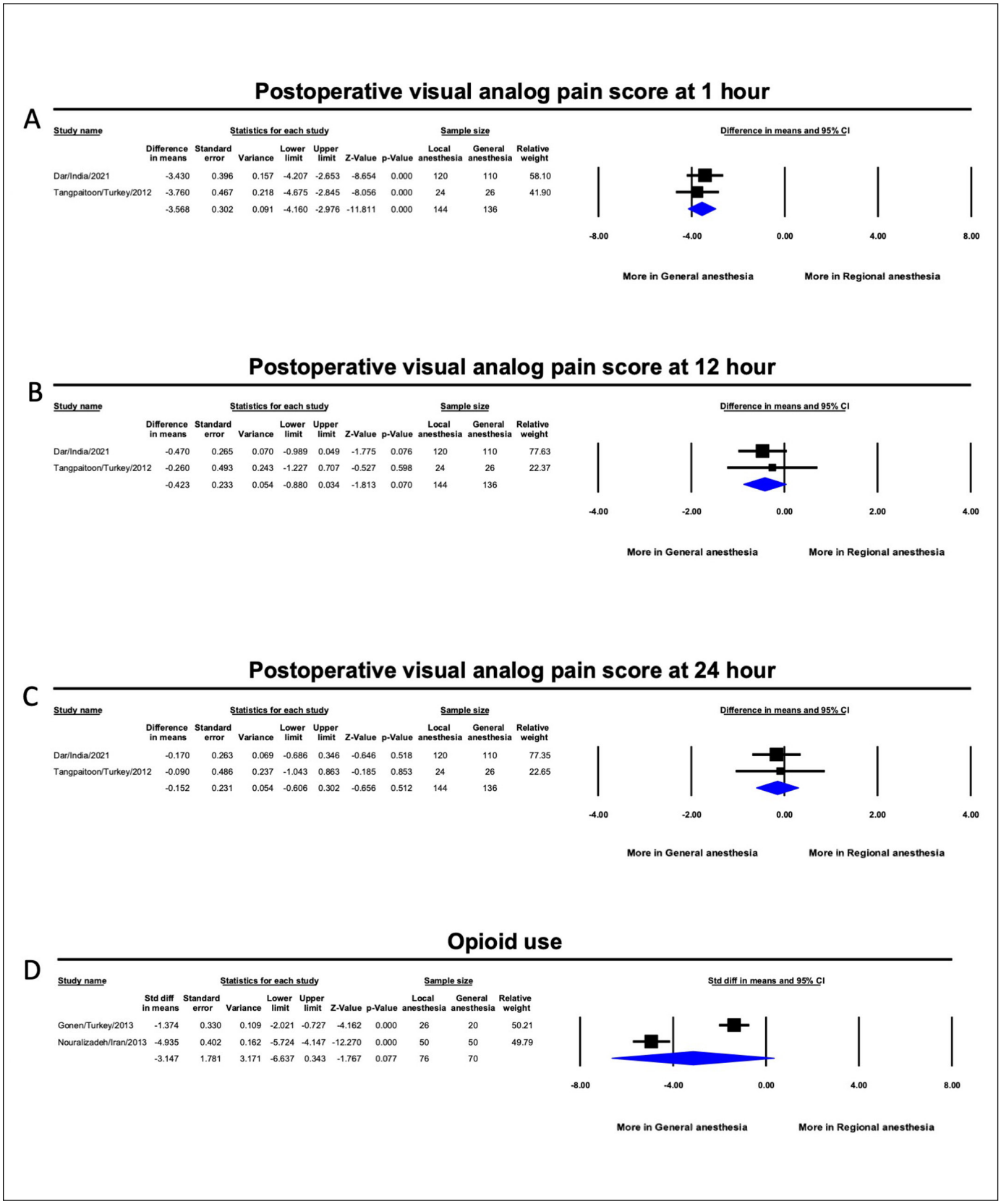

Figure 3. *Forest plots for the meta-analysis comparing the outcomes of percutaneous nephrolithotomy patients between regional anaesthesia and general anaesthesia groups:* **(a)** *Postoperative visual analog pain score at 1 hour;* **(b)** *Postoperative visual analog pain score at 12 hours;* **(c)** *Postoperative visual analog pain score at 24 hours;* **(d)** *Opioid use.*

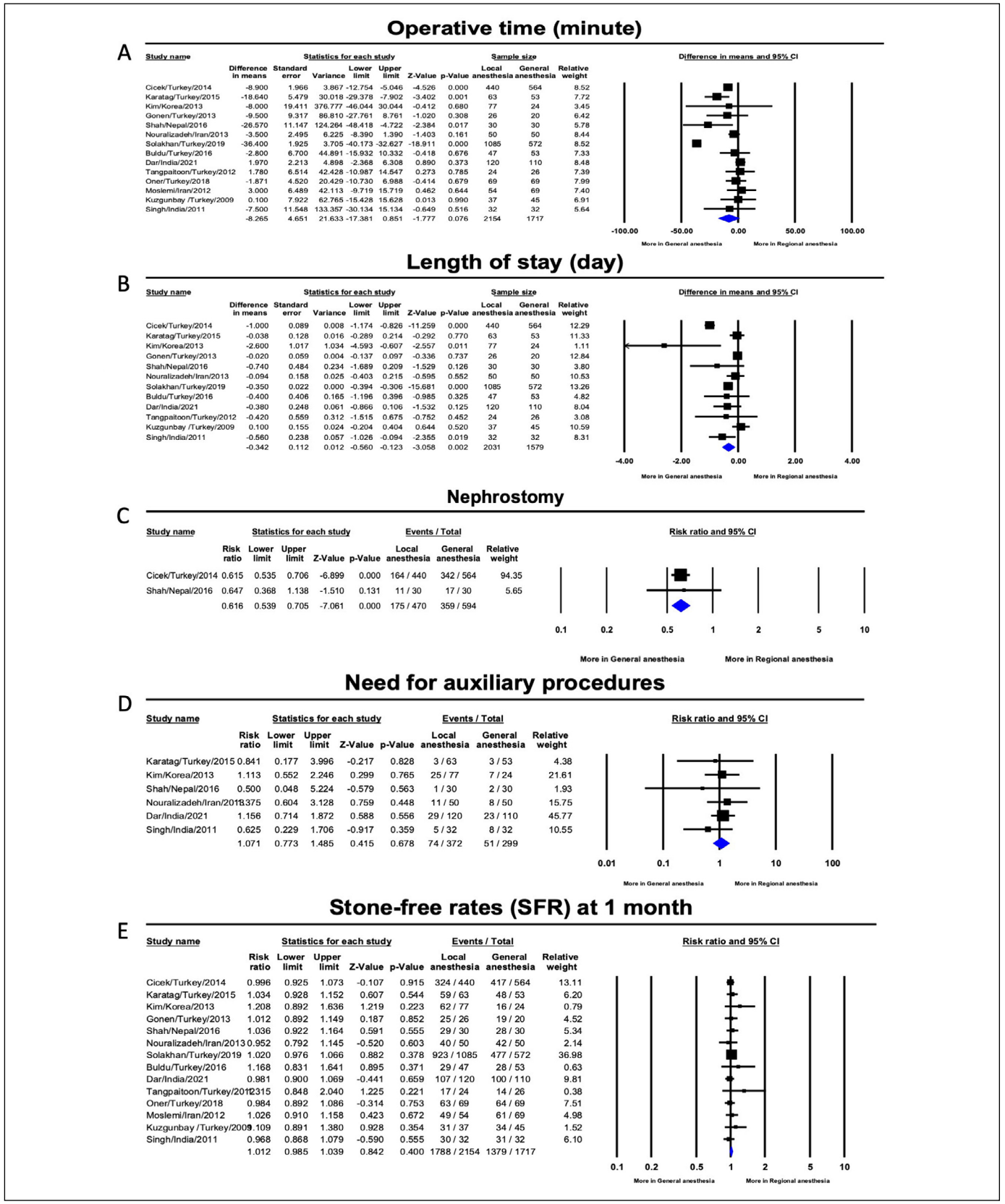

Figure 4. *Forest plots for the meta-analysis comparing the outcomes of percutaneous nephrolithotomy patients between local anesthesia and general anaesthesia groups:* **(a)** *Operative time;* **(b)** *Length of stay;* **(c)** *Nephrostomy;* **(d)** *Need for auxiliary procedures;* **(e)** *Stone-free rates (SFR) at 1 month.*

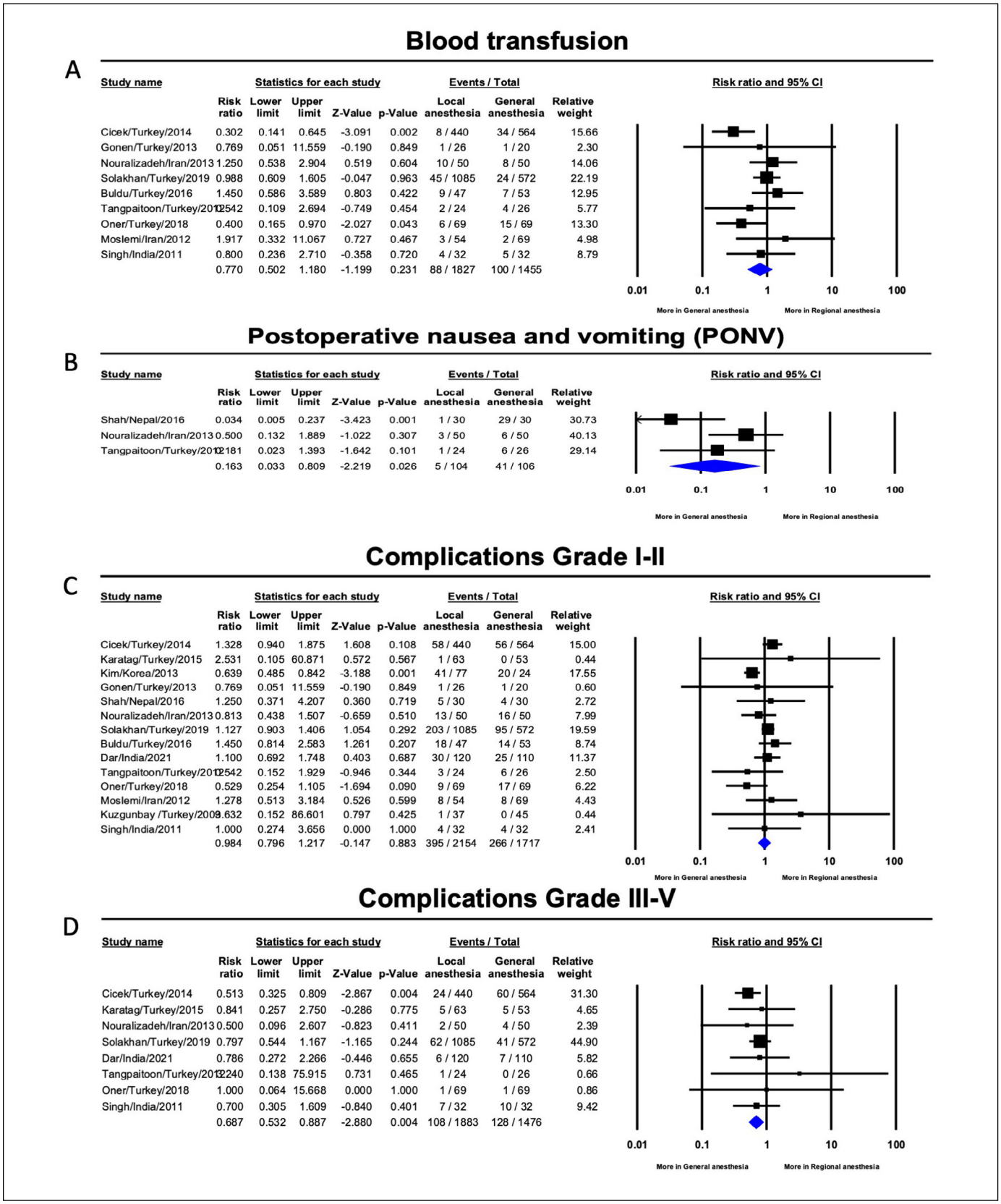

Figure 5. *Forest plots for the meta-analysis comparing the outcomes of percutaneous nephrolithotomy patients between regional anesthesia and general anesthesia groups:* **(a)** *Blood transfusion;* **(b)** *Postoperative nausea and vomiting (PONV);* **(c)** *Complications Grade I–II;* **(d)** *Complications Grade III–V.*

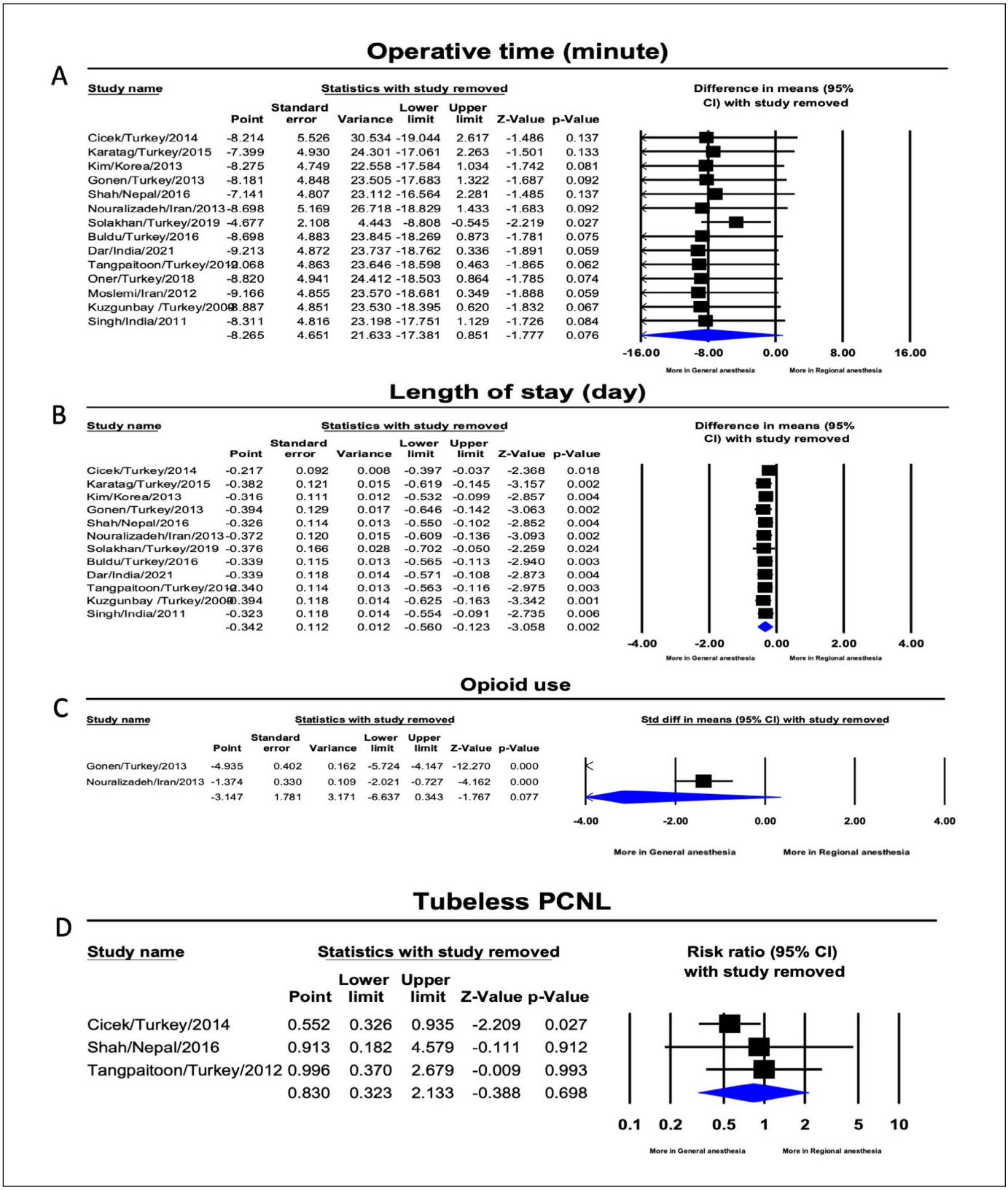

Figure 6. *Forest plots for the sensitivity analysis by the "one-study-removed" procedure comparing the outcomes of percutaneous nephrolithotomy patients between regional anesthesia and general anesthesia groups:* **(a)** *Operative time,* **(b)** *Length of stay,* **(c)** *Opioid use,* **(d)** *Tubeless percutaneous nephrolithotomy.*

PCNL – percutaneous nephrolithotomy

p = 0.041), a higher BMI (MD = 0.9, 95% CI 0.51 to 1.29, p <0.001), a shorter length of stay (MD = -0.34 days, 95% CI -0.56 to -0.12, p = 0.002), lower nephrostomy rates (RR = 0.61, 95% CI 0.5 to 0.7, p <0.001), lower postoperative nausea and vomiting rates (RR = 0.16, 95% CI 0.03 to 0.80, p = 0.026), lower complications grade III–V rates (RR = 0.68, 95% CI 0.52 to 0.89, p = 0.006), and lower postoperative visual analogue pain score (VAS) at 1 hour (MD = -3.5, 95% CI -4.1 to -2.9, p<0.001) [9–22]. There were no significant differences in other outcomes between the two groups, including the size of the stone, stone burden, operative time, need for auxiliary procedures, stone-free rates (SFR) at 1 month, blood transfusion, complications grade I–II, postoperative visual analogue pain score at 12 hours, postoperative VAS at 24 hours and opioid use (Table 2, Figures 1–5) [23].

The heterogeneity of the operative time, length of stay, and opioid use was high (I^2 = 94%, 89%, and 94%, respectively). We used sensitivity analysis to assess the heterogeneity (Figure 6).

Risk of bias assessment

The NOS tool was used to evaluate the study's quality. Most of the included studies were retrospective (n = 8), with five randomised studies [9, 10, 13, 17, 19]. The number of stars awarded to each included study ranged from six to nine. Details of the given stars within each NOS domain are shown in Table 3.

Publication bias

We used Egger's regression test to assess the publication bias, and it did not suggest any evidence of bias, as confirmed by Egger's regression test (p = 0.896). Moreover, the funnel plot showed no evidence of asymmetry (Figure 7).

DISCUSSION

In the minimally invasive therapy era, urologists have made great efforts in modifying the technique to increase the safety, efficacy, and outcomes of PCNL. Previous meta-analyses have been per-

Table 3. *Quality assessment for the included studies*

Author/country/year	Selection				Comparability of cohorts		Outcome			Total
	Representative of the exposed cohort	Selection of external control	Ascertainment of exposure	Outcome of interest not present at the start of the study	Main factor	Additional factor	Assessement of outcomes	Sufficient follow-up time	Adequecy of follow-up	
Singh/India/2011 [9]	*	*	*	*	*	*	*	*	0	8
Kuzgunbay /Turkey/2009 [10]	*	*	*	*	*	*	*	*	0	8
Moslemi/Iran/2012 [11]	*	0	*	*	*	0	*	*	0	6
Oner/Turkey/2018 [12]	*	0	*	*	*	0	*	*	0	6
Tangpaitoon/Turkey/2012 [13]	*	*	*	*	*	*	*	*	0	8
Dar/India/2021 [14]	*	*	*	*	*	*	*	*	*	9
Buldu/Turkey/2016 [15]	0	*	*	*	*	*	*	*	0	7
Solakhan/Turkey/2019 [16]	*	*	*	*	*	*	*	*	0	8
Nouralizadeh/Iran/2013 [17]	*	*	*	*	*	*	*	*	0	8
Gonen/Turkey/2013 [18]	*	0	*	*	*	*	*	*	*	8
Shah/Nepal/2016 [19]	*	*	*	*	*	*	*	*	0	8
Kim/Korea/2013 [20]	*	0	*	*	*	0	*	*	0	6
Cicek/Turkey/2014 [21]	*	*	*	*	*	0	*	*	0	7
Karatag/Turkey/2015 [22]	0	*	*	*	*	*	*	*	0	7

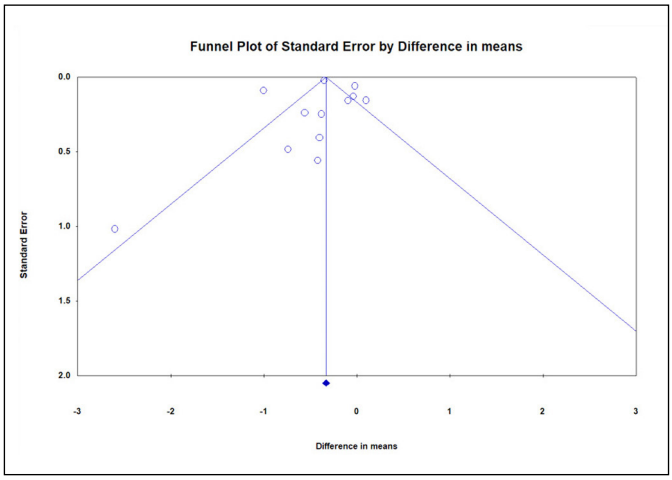

Figure 7. *Funnel plot shows no evidence of asymmetry which was further confirmed by the Egger's regression test (p = 0.896).*

formed to evaluate the impact of different anaesthesia modalities on PCNL outcomes [24–26]. However, in the last four years, there have been some new studies with larger data published as well as changes in clinical practice, our recent meta-analysis could provide updated evidence and evaluate the current outcomes.

Firstly, our recent study found that the patients undergoing regional anaesthesia had a significantly higher age and BMI compared to those under general anaesthesia [16, 20, 22]. This finding indicated a difference between these two approaches in patient selection, which is an important factor to consider. Regional anaesthesia is an optimal option in patients with higher age and BMI, who have a higher risk of respiratory and cardiovascular events, and anaesthesia-related complications.

Secondly, our results found that regional anaesthesia had a lower postoperative nausea and vomiting rate and a lower immediate postoperative visual analog pain score [13, 14, 19]. Although these two approaches had no significant difference in postoperative visual analog pain score at 12 hours and 24 hours, these findings indicate the advantages of regional anaesthesia compared to general anaesthesia in PCNL. These results are consistent with a previous meta-analysis [25]. In our study, we also found that the regional anaesthesia group had a shorter stay length than the general anaesthesia group [27]. In addition, regional anaesthesia patients also offer a lower cost of anaesthesia and better health-economic benefits [28].

Thirdly, regarding surgical outcomes, the regional anaesthesia group had a lower nephrostomy rate and lower complications grade III–IV rates with the same size of stone and stone burden, and the similar efficacy in operative time, blood transfusion, complication grade I–II, need for the auxiliary procedure, and SFR at 1 month [13, 21].

Overall, our study highlights some advantages of regional anaesthesia compared to general anaesthesia, such as lower postoperative nausea and vomiting rates, lower complication grade III–IV rates, and a shorter length of stay. Furthermore, patient selection plays an important role when choosing anaesthesia techniques, which depends on individual patient characteristics and possibly patient counselling.

The meta-analysis study design of this study has some inherent limitations. The included studies used various regional anaesthesia approaches, puncture types, sheath sizes, and lithotriptor types, resulting in heterogeneity. Furthermore, the short-term follow-up of the published studies limits the comparison of long-term outcomes, although this may be a minor concern as early outcomes should be validated before comparing longer-term results with new approaches. Finally, the regional anaesthesia group used different anaesthesia levels in the included studies. Despite these limitations, this study is the most comprehensive meta-analysis of the subject; It provides health systems and surgeons with insights into the potential benefits of regional anaesthesia in PCNL.

CONCLUSIONS

Our results show that PCNL under regional anaesthesia is safe and feasible, with comparable results to those under general anaesthesia. While the results are similar, PCNL under regional anaesthesia had a reduced rate of postoperative nausea and vomiting, immediate post-operative pain, major complications, and length of hospital stay. While patient selection is important, counselling and decision-making for these procedures must go hand in hand to achieve the best clinical outcomes.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL PAPER

TRAUMA AND RECONSTRUCTIVE UROLOGY

The role of gel-infused translabial ultrasound as a new modality in evaluation of female urethral stricture

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Introduction To investigate the role of trans-labial ultrasound study in detection of female urethral stenosis (FUS) compared to former cysto-urethroscopy as the currently available definitive diagnostic modality.

Material and methods In this cross-sectional study, 60 consecutive patients with bladder outlet obstruction diagnosed by clinical symptoms and urodynamic study, were included from 2019 to 2022. For additional assessment, all these patients underwent gel-Infused trans-labial ultrasound (GITLUS) and cystourethroscopy. Trans-labial real-time ultrasonography was performed following the insertion of 20 ml steady stream viscous jelly into the urethral meatus to assess the length of the urethra and exact location and length of the probable narrowing, as well as the presence of peri-urethral fibrosis (PUF).

Results In GITLUS evaluation, urethral stricture was found in 27 patients. Mean urethral length and stricture length were 35.63 ±4.78 and 17.04 ±10.59, respectively. All these stenosis were confirmed via cysto-urethroscopy. PUF was found in 20 of 27 patients. In cysto-urethroscopy, urethral stricture was confirmed in 40 patients: 13 in urethral meatus and 27 in other parts or pan-urethra. GITLUS could not reveal urethral stricture in 13 patients with meatal stenosis, confirmed with cystoscopy. GITLUS detected FUS less accurately when it involves pure distal urethra compared to other parts of urethra or pan-urethral stenosis (p value = 0.002).

Conclusions GITLUS is a safe, non-invasive, and valuable technique for detecting FUS. The location and the length of the stricture and probable peri-urethral fibrosis can be identified by this method. However, in meatal or pure short-length distal urethral strictures, this method should be used with caution.

Key Words: urethral stricture ‹› ultrasound ‹› female ‹› cystoscopy ‹› urodynamic ‹› urethroplasty

INTRODUCTION

Bladder outlet obstruction (BOO) is an uncommon cause of female lower urinary tract symptoms (LUTS) with an estimated prevalence of 2.7-8%. Female urethral stricture (FUS) is an even more rare condition that accounts for 4-18% of the patients with so called BOO [1, 2]. According to the low prevalence of urethral stricture in women, there is no widely accepted consensus on the definition of FUS and its diagnostic criteria in the literature. Osman NI et al defined urethral stricture as an anatomical and symptomatic narrowing of the urethra that does not accommodate urethral instrumentation and can be confirmed by visual inspection, urethral calibration, urethroscopy or imaging studies [3]. Some researchers described FUS as a fixed anatomical narrowing (<14F) between distal urethra and the bladder neck [4]. There are several causes for FUS including iatrogenic conditions, history of inflammation and urethritis, chronic cystitis, stone passage, malignancy, trauma, radiation and idiopathic. Prolonged

catheterization and repeated instrumentation are the most common causes responsible for iatrogenic urethral strictures [5].

LUTS in women is multifactorial and may result from both anatomical and functional disorders. Obstructive LUTS in women may present with several symptoms including weak urinary stream, straining, nocturia, incomplete emptying, dribbling, hesitancy, and even urinary retention as a result of BOO [6]. Women with underactive bladder may present with similar symptoms [7] and clinicians should be aware of it as a probable cause of voiding dysfunction and LUTS. Diagnosis of FUS requires clinical suspicion, obtaining detailed medical history and thorough evaluation including: physical examination and specific para-clinics including urodynamic study or cystoscopy [8]. In a systematic review of 40 studies [3], uroflowmetry, measurement of post-void residual urine (PVR), cysto-urethroscopy, voiding cysto-urethrogram (VCUG), urodynamics, video urodynamics, and magnetic resonance imaging (MRI) were utilized to diagnose FUS. In a limited case series study, Sussman et al [9] introduced a gel-infused trans-labial ultrasound (GITLUS) as a novel technique to characterize female urethral stenosis, for the first time.

In the present study, we aimed to investigate the role of trans-labial ultrasound study in detection of urethral stenosis and distinguish it from other causes of female LUTS; furthermore, evaluating the practical value of this method in comparison to former cysto-urethroscopy as the currently available definitive diagnostic modality.

MATERIAL AND METHODS

Patients and setting

This cross-sectional study was conducted in our referral center from 2019 to 2022. Females with obstruc-

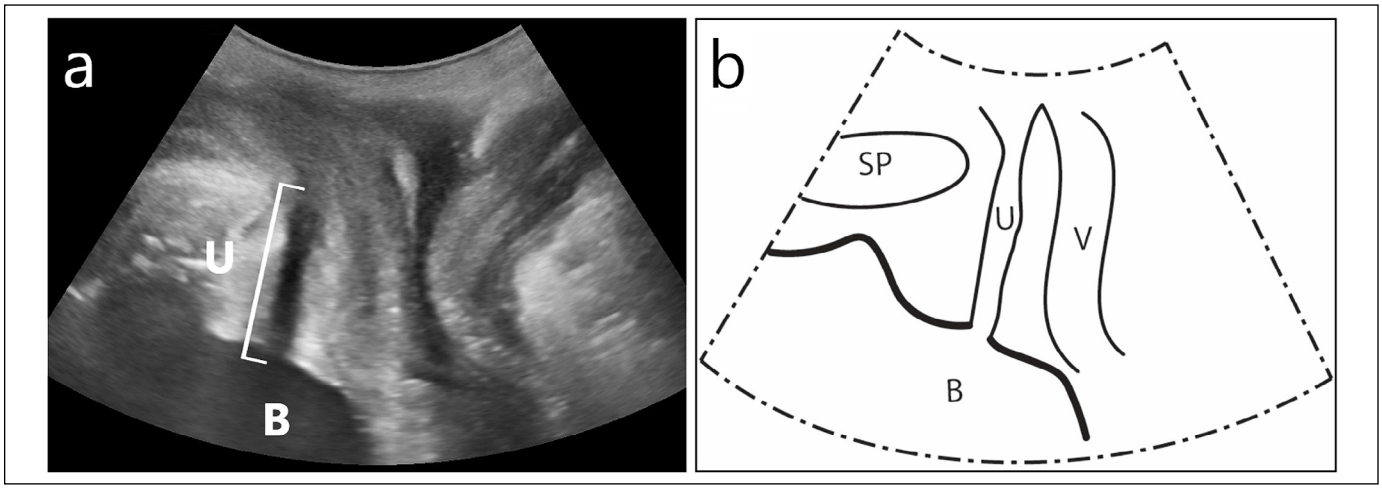

Figure 1. *Gel-infused trans-labial ultrasound of normal urethra* **(a)***; Schematic view of the same patient* **(b)***.*

U – urethral length; B – bladder; U – urethra; SP – symphysis pubis; V – vagina

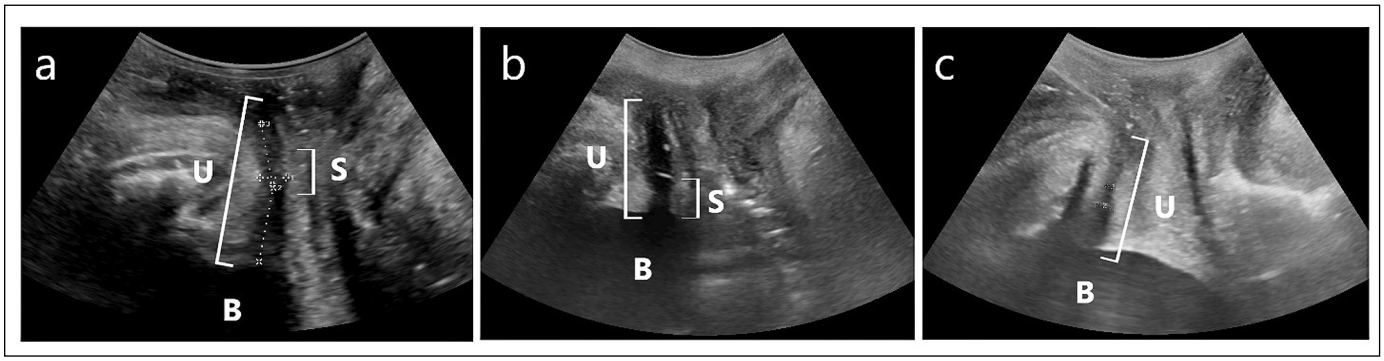

Figure 2. *Mid-urethral stricture* **(a)***; Proximal urethral stricture* **(b)***; Pan-urethral stricture and peri-urethral fibrosis demonstrating as hyper-echoic tissue surrounding the urethra* **(c)***.*

U – urethral length; B – bladder; S – stricture

tive LUTS lasting for at least 6 months and failed conservative and medical treatment were included in this study. The presence of grade 3 cystocele or rectocele, untreated urinary tract infection, para-urethral cysts, urethral prolapse, urethral diverticula, spinal cord injury or any known neurologic disease and lack of patients' consent to participate were considered as exclusion criteria. The study was approved by the research Ethics Committees of SBMU School of Medicine, (IR.SBMU.MSP.REC.1400.613). Written informed consent was obtained from all participants prior to the study which was in accordance with the ethical standards of the 1964 Deceleration of Helsinki as revised in 2000.

After primary evaluation including medical history and physical examination of 79 consecutive patients complaining of obstructive urinary symptoms by an expert female urologist, all patients underwent a multi-channel urodynamic study in maximum patient dignity and privacy. Pressure-flow study during the voiding phase was performed. Maximum urinary flow rate (Qmax), PVR volume and detrusor pressure at maximum urinary flow (Pdet@Qmax) were recorded. Bladder contractility index (BCI) was used to distinguish outflow obstruction and detrusor underactivity (DU). Nineteen patients with BCI<100 were considered as DU and excluded from the study. For remaining 60 patients (mean age: 55.6 ±12.8 years), additional tests including GITLUS and cystourethroscopy were performed.

For assessment of the urethra with GITLUS, patients were asked to have a comfortably full bladder. While the participants were lying in the supine and low lithotomy position, the CA1-7A convex array probe (Samsung WS80) was placed on just off midline trans-labial region in a sagittal plane. Real-time ultrasonography was performed by an expert radiologist. Before the procedure, the inter-labial area was sterilized, and then 20 ml of steady stream viscous jelly (lidocaine 2%) was inserted into the urethral meatus using a needle-less syringe.

The goals were assessing the length of the urethra, and exact location and length of the probable narrowing, as well as presence of peri-urethral fibrosis (PUF). (Figure 1, 2)

Urethral stricture in cystoscopic evaluation was defined by failure to pass a 14-French cystoscope sheath through any part of the urethra. Since the exact border of the different parts of the female urethra could not be addressed accurately in cystourethroscopy, the location of the urethral stricture was categorized as 1/3 distal (pure distal urethral or meatal stricture) and any other parts of the urethra including the combined or pan urethral strictures.

Statistical analysis

Quantitative data are shown as mean and standard deviation (SD) for data with normal distribution. The normality of the data was tested using the Kolmogorov-Smirnov test. Categorical data were shown as frequency. We utilized SPSS version 21.0 software (IBM Corporation, Armonk, NY, USA) for statistical analysis. Two tailed P-values < 0.05 were considered for the statistical level of significance.

RESULTS

A total of 79 patients meeting inclusion criteria, were enrolled in the study. Urodynamic study revealed low bladder contractility index (BCI) in 19 patients which was compatible with DU and the patients were excluded from the study. The remaining 60 patients were candidate for GITLUS and cysto-urethroscopic evaluation. Mean patients' age was 55.6 12.8 years

Table 1. *Demographic data of the patients*

	Yes	No
History of NVD	41	19
History of C/S	19	41
History of retention	2	58
History of urethral dilatation	23	37
Diabetes mellitus	8	52
History of recurrent UTI	10	50
Cystocele grade 1 or 2	25	35
Rectocele grade 1 or 2	18	42
Menopause	35	25

NVD – normal vaginal delivery; C/S – cesarean section; UTI – urinary tract infection

Table 2. *Gel-infused trans-labial ultrasound findings in 27 patients diagnosed with urethral stricture*

Mean Urethral length (mm ±SD)	35.63 ±4.78
Mean stricture length (mm ±SD)	17.04 ±10.59
Mean length from meatus to distal part of stricture (mm ±SD)	9.33 ±7.48
Mean length from proximal part of stricture to bladder neck (mm ±SD)	8.81 ±7.41
Stricture location in urethra	
Proximal	1
Middle	10
Distal	0
Proximal and middle	1
Middle and distal	10
Pan-urethra	5
Peri-urethral fibrosis	20

SD – standard deviation

and mean BMI was 25.2 ±3.1. Demographic data is summarized in Table 1.

Urodynamic study revealed detrusor over-activity in 12 patients. In patients with bladder outlet obstruction index (BOOI) of more than 40, the mean Qmax and Pdet@Qmax were 9.6 ±4.06 and 47.3 ±.3, respectively. Twenty-two patients had PVR ≥150cc, 17 participants had PVR ≤100cc and in remaining 21, PVR was between 100–150 cc. In GITLUS, urethral stricture was found in 27 patients. Mean urethral length and mean stricture length were 35.63 ±4.78 and 17.04 ±10.59 respectively (Table 2). All of these stenoses were confirmed through cysto-urethroscopy. PUF was found in 20 out of 27 patients with stenosis. During cysto-urethroscopy, urethral stricture was confirmed in 40 patients: 13 in urethral meatus or distal urethra and 27 patients with strictures located in other parts of the urethra including proximal, mid, combined parts or pan urethra. Fixed urethra, pale mucosa and bladder wall trabeculation were seen in 30, 36 and 14 patients, respectively. Twenty participants did not have urethral stricture. GITLUS was able to correctly report all 20 patients with normal cystoscopic evaluation. However, ultrasound studies were unable to detect urethral strictures in 13 patients with meatal stenosis or short-length pure distal strictures, as confirmed by cystoscopy. GITLUS, on the other hand, proved to be more accurate in detecting urethral strictures that did not involve the urethral meatus or pure distal urethra ($p = 0.002$).

DISCUSSION

Urethral stricture as a rare cause of female voiding dysfunction is likely underestimated and underreported. FUS has a broad spectrum of clinical manifestations and a high index of suspicion is needed to look for further evaluation [10]. Lack of a universally accepted definition and diagnostic criteria for FUS is another issue in female urology era. Previously, several techniques have been reported to evaluate FUS, including MRI, VCUG, uro-flowmetry study, urethral calibration and cysto-urethroscopy. In the evaluation of 70 male patients with LUTS, Choudhary S et al [11] found that ultrasound study is as effective as retrograde urethrogram (RUG) in diagnosis of anterior urethral strictures. In addition, ultrasound study had more accuracy in detection of fibrosis, length and diameter of the stenosis; and when compared to RUG, it was associated with less discomfort, pain and bleeding. In a small case series, Sussman et al (9) introduced GITLUS as a novel technique to identify FUS. In their study, 8 patients with previous history of urethral stricture whom were diagnosed by uroflowmetry, PVR, video urodynamics, and cystoscopy, underwent GITLUS. They found GITLUS as a safe, valuable and accurate tool in diagnosis of FUS.

In our study, all the strictures limited to the proximal, middle parts or pan urethra as well as distal plus mid urethra were detected by GITLUS. However, 13 out of 40 patients with strictures involving the pure distal part of the urethra or urethral meatus were missed by this method. We believe this could be due to a technical problem; when the syringe was inserted into the urethra, it may bypass the meatus or short-length distal urethral strictures causing false-negative results. Considering the above, in patients complaining of persistent obstructive LUTS, even with normal GITLUS, pure distal or meatal strictures should be re-evaluated with cysto-urethroscopy and direct visual examination.

Although cysto-urethroscopy is a relatively invasive test, it brings us the opportunity for localization and treatment of the probable FUS at the same time. However, if we are not careful

enough, passing the cystoscope through the short strictures can cause false-negative results. Moreover, in case of inability to pass the stricture during cystoscopy, estimating the length of the stricture would not be possible. Ultrasound study and detection of the location and length of the stricture would be very helpful for surgical planning. Evaluating the peri-urethral tissue and detecting the probable PUF is another special feature of ultrasound study in comparison to other diagnostic tests including cysto-urethroscopy or urodynamic study.

Sussman et al [9] found PUF in all 8 cases with urethral stricture, but due to the small sample size, they could not confirm the role of this finding in predicting prognosis. Vashishtha S et al [12] in evaluation of 52 patients up to 18 years old, concluded that PUF, stricture length, associated para-urethral abscess and etiology of the stricture would have a great impact on overall prognosis and success rate of the urethroplasty. In the present study, we found PUF in 20 of 27 patients diagnosed with urethral stricture by ultrasound study. Fifteen (75%) patients with PUF had history of at least two times previous urethral dilatations which may indicate PUF as a prognostic factor for treatment failure. However, a well-designed study with larger sample size would be required to prove the claim. The ability of GITLUS to identify the normal urethra is of particular importance. It can be used as the first diagnostic modality to rule out FUS in selected patients in order to prevent unnecessary invasive tests.

GITLUS has some benefits over transvaginal ultrasound study including the ability to perform it in pediatric, pregnant, and virgin patients. Moreover, in TV-US un intentional pressure to the urethra may

cause false positive results. GITLUS is also safer in terms of radiation exposure and anesthesia risk in pregnant or high-risk patients, when compared to other diagnostic techniques such as VCUG, RUG or cysto-urethroscopy. However, a limitation of this method could be the need to a trained, expert and experienced radiologist in evaluating the female urethra. We recommend performing GITLUS only in tertiary referral centers with high patient volume. The strength of this study is its relatively large sample size, which is rare for FUS. However, in order to address the pitfall of GITLUS in detecting meatal and distal urethral strictures, it is strongly suggested that the technique be re-evaluated and solutions be found for better visualization of the entire female urethra.

CONCLUSIONS

GITLUS is a safe, non-invasive, and valuable technique for detecting FUS. The strengths of this modality include the lack of need for anesthesia, ionizing radiation, and urethral catheterization.
It can accurately identify the location and length of the stricture. Additionally, it can evaluate peri-urethral pathologies such as PUF, which can be important for surgical planning and outcome. However, in meatal or pure short length distal urethral strictures, this method should be use with caution.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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VIDEOABSTRACT

VIDEOSURGERY

Video can be found at https://ceju.online/journal/2023/Penile-Urethrostomy-urethral-stricture-Reconstructive-Surgery--2305.php

Penile urethrostomy for recurrent long-segment strictures of the penile urethra: step-by-step surgical technique

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Key Words: penile urethrostomy ‹› urethral stricture ‹› reconstructive surgery ‹› minimal invasive technique

In cases of recurrent long-segment urethral strictures (US), the minimally invasive variant of a perineal urethrostomy can be offered as an alternative to an augmentation urethroplasty. Patients who do not desire extensive urethral reconstruction or are unable to undergo a long surgery are ideal candidates for this surgery. The main disadvantage of perineal urethrostomy is that patients can subsequently urinate only while sitting. However, some males have a strong desire to keep voiding standing. For this group of patients and under the condition that the stricture is located only along the penile urethra, a penile urethrostomy may be offered.

In this video, we present step-by-step description of the surgical technique of a penile urethrostomy as an independent surgery, not as part of a staged urethroplasty.

In the current case, a 51-year-old patient with a long penile US after numerous previous surgeries desired a definite solution without the use of any graft. Due to his strong desire to keep voiding in a standing position, he opted for a penile urethrostomy.

A method of localizing the proximal margin of the US is to insert a 4 Fr. ureteral occlusion catheter (Urotech®) deep into the bulbar urethra, block it with 3 cc of saline, and gently pool it back until resistance is encountered.

An inverted u-shaped fasciocutaneous flap is raised at this level, and the penile urethra is dissected.

Between stay sutures the ventral side of the healthy urethra is longitudinally incised. An opening should be made in the urethra at least 3 cm long to create a wide urethrostomy.

Optionally, the proximal urethra may be calibrated with a 30 Fr. bougie, especially when the preoperative urethrogram is inconclusive.

The urethrocutaneous anastomosis is performed using interrupted 3.0 polyglactin (Vicryl™) sutures. It is crucial to incorporate the skin, the urethral mucosa, and the adventitia of corpus spongiosum separately in these anastomosis sutures to achieve better haemostasis without compromising the blood supply within the periurethral spongy tissue.

This step may be modified by first placing a running suture 4.0 polydioxanone (PDS™) connecting the urethral mucosa with the adventitia of the corpus spongiosum on each side before approximating the skin. This technique should be preferred in cases of excessive bleeding to allow better visualization.

In cases where the penile urethrostomy is created in the penoscrotal junction, attention should be given to a tension-free reconstruction of the skin without changing the preoperative level and

angle of the penoscrotal junction, allowing urination in a standing position without wetting the patients' scrotum and with a pleasing aesthetic result.

A 16 Fr. silicone Foley catheter is inserted into the bladder and remains in place for 7 days.

Concluding, penile urethrostomy is a straightforward procedure with a satisfactory aesthetic outcome, which could be considered an equivalent alternative to perineal urethrostomy for patients with penile US who wish to keep voiding while standing.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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VIDEOABSTRACT

VIDEOSURGERY

Video can be found at https://ceju.online/journal/2023/robotic-tumour-thrombus-cavotomy-nephrectomy-and-IVC-thrombectomy-2313.php

Robotic left nephrectomy with level IV inferior vena cava thrombectomy using the AngioVac system

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Key Words: robotic ‹› tumour thrombus ‹› cavotomy ‹› nephrectomy and IVC thrombectomy ‹› AngioVac system

We report the first successful elective procedure of atrial thrombus aspiration with the AngioVac System (AVS) and robotic-assisted level IV inferior vena cava (IVC) tumour thrombectomy in a left renal carcinoma.

A 75-year-old male presented with 7.2 cm left renal tumour and a level IV IVC tumour thrombus (13.4 cm length) extending into the right atrium for 3.8 cm without distant metastasis.

We decided to combine AVS of aspiration (for the intra-atrial thrombus component treatment) with robotic surgery (for the left nephrectomy and IVC thrombectomy). VV-ECMO (right jugular – right femoral vein) was performed with mild heparinization (ACT target 190), and the AngioVAC catheter was inserted from the right jugular vein to the right atrium, targeting the thrombus. Atrial thrombus aspiration was performed under transoesophageal echocardiography (TEE) control. An intraoperative cavography and a total body CT scan, performed 2 days after the AngioVac procedure, confirmed the absence of the thrombus in the atrium, showing a level IIIa IVC-thrombus.

After one week, the two-step robotic procedure started with the left radical nephrectomy and subsequently concluded with cavotomy and complete removal of the tumour thrombus (confirmed by ECD-sonography). The AngioVAC system aspiration operative time was 210 minutes. The Robotic Nephrectomy and IVC thrombus removal operative time was 560 minutes with 300 cc of blood loss. The patient's hospital stay after the nephrectomy and cavotomy was 9 days. The definitive pathology showed a stage pT3b clear cell carcinoma, Fuhrman grade III, with 8 cm neoplastic thrombus. The length of the neoplastic thrombus aspirated with the AngioVAC system was not evaluable. The use of the AngioVac system transformed the IVC thrombus from level 4 to level 3, thereby avoiding the need for a sternotomy. This approach ensures a highly multidisciplinary and complex surgery in a procedure that is as minimally invasive as possible.

AngioVAC aspiration of intra-atrial thrombus combined with robotic surgery as an elective indication is a safe procedure for minimally invasive

left nephrectomy with level IV inferior vena cava thrombectomy.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

VIDEOABSTRACT

VIDEOSURGERY

Video can be found at https://ceju.online/journal/2023/simple-prostatectomy-SinglePort-bladder-diverticulum-2306.php

Transperitoneal single-port robotic Firefly-guided bladder diverticulectomy and simple prostatectomy

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Key Words: simple prostatectomy ‹› Single-Port ‹› bladder diverticulum

Single-port (SP) robotic assisted simple prostatectomy (RASP) is preferably performed via a trans-vesical approach which allows avoiding breach into the peritoneal cavity, reducing bowel-associated surgical morbidity, while simultaneously providing immediate access to the prostatic adenoma. Nonetheless, in specific surgical scenarios, a transperitoneal approach can be preferred.

We present a case of a 76-year-old man who underwent transperitoneal SP-RASP and Firefly-guided Diverticulectomy at Rush University medical center in August 2023. Pre-operative computer tomography (CT) imaging revealed an indwelling Foley catheter and an enlarged prostate with an estimated volume of 85cc. Additionally, a diverticulum measuring 3.5 cm in diameter was observed on the upper left aspect of the bladder wall, accompanied by moderate bilateral hydronephrosis. In this specific case, the trans-vesical approach was deemed to be suboptimal due to the location of the diverticulum which was thought to increase the likelihood of potential adhesions of the diverticulum with intestinal loops, thereby raising the risk of associated bowel injury during a diverticulectomy via a trans-vesical approach. Thus, in this specific scenario, we opted for the transperitoneal approach. A 4 cm midline incision just above the umbilicus which offered safer and more immediate surgical access to the diverticulum, as well as an optimal working angle to address both operative targets: the diverticulum and the adenoma. During the surgery, the camera was typically positioned at twelve o'clock with monopolar curved scissors at three o'clock, fenestrated bipolar forceps at nine o'clock, and Cadiere forceps at six o'clock. Intraoperative flexible transurethral cystoscopy facilitated – switching to da Vinci Firefly® vision modality – accurate localization of the diverticulum and enabled faster and more efficient isolation, reducing the risk of its premature opening. The ROSI device plays a key role during adenoma enucleation, allowing for suction and countertraction. The procedure was successfully completed without intraoperative complications: Operative time was 300 minutes, Estimated Blood Loss was 50 ml. No drain was placed and no continuous bladder irrigation was needed post-operatively. The hospital stay was 36 hours. The catheter was removed on the 9th postoperative day, without a cystogram.

SP-RASP is a safe, effective, and reproducible procedure for the treatment of large prostate gland, especially in presence of concomitant bladder pathologies. While a trans-vesical approach is usu-

ally preferred to perform the procedure, in specific scenario the surgeon can adopt a different surgical strategy. In case of large diverticula located in the upper part of the bladder, a transperitoneal approach might minimize the risk of injuring intraabdominal organs.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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